DEPARTMENT OF OBST & GYNAE

INTRA VAGINAL MISOPROSTOL VERSUS INTRA CERVICAL DINOPROSTONE IN MID-TRIMESTER ABORTION

THESIS

FOR MASTER OF SURGERY
(OBSTETRICS & GYNAECOLOGY)

BUNDELKHAND UNIVERSITY
JHANSI (U.P.)

SHIKHA SINGH

2004

Certificate

****

*This is to certify that the work entitled "**INTRAVAGINAL MISOPROSTOL VERSUS INTRACERVICAL DINOPROSTONE IN MID-TRIMESTER ABORTION**" which is being submitted as a thesis for **M.S. (Obstetrics and Gynaecology)** examination, 2004 under Bundelkhand University by **Dr. SHIKHA SINGH,** has been carried out in the department of Obstetrics and Gynaecology, M.L.B. Medical College, Jhansi under my direct supervision and guidance. The observations recorded have been checked and verified by me from time to time.*

She has put in the necessary stay in the department as per required by the regulations of Bundelkhand University.

Dated :

(Dr. MRIDULA KAPOOR)
M.S.,
Professor and Head
Department of Obstetrics and Gynaecology
M.L.B. Medical College, Jhansi (U.P)

Certificate

****

This is to certify that the work entitled ***"INTRAVAGINAL MISOPROSTOL VERSUS INTRACERVICAL DINOPROSTONE IN MID-TRIMESTER ABORTION"*** *which is being submitted as a thesis for* ***M.S. (Obstetrics and Gynaecology)*** *examination, 2004 under Bundelkhand University by* ***Dr. SHIKHA SINGH,*** *has been carried out in the department of Obstetrics and Gynaecology, M.L.B. Medical College, Jhansi under my direct supervision and guidance. The observations recorded have been checked and verified by me from time to time.*

Dated :

(Dr. USHA AGARWAL)
M.S.,
Professor,
Department of Obstetrics and Gynaecology
M.L.B. Medical College, Jhansi (U.P)
(Guide)

Certificate

****

*This is to certify that the work entitled "**INTRAVAGINAL MISOPROSTOL VERSUS INTRACERVICAL DINOPROSTONE IN MID-TRIMESTER ABORTION**" which is being submitted as a thesis for **M.S. (Obstetrics and Gynaecology)** examination, 2004 under Bundelkhand University by **Dr. SHIKHA SINGH,** has been carried out in the department of Obstetrics and Gynaecology, M.L.B. Medical College, Jhansi under my direct supervision and guidance. The observations recorded have been checked and verified by me from time to time.*

Dated :

(Dr. SUSHILA KHARKWAL)
M.D.,
Associate Professor,
Department of Obstetrics and Gynaecology
M.L.B. Medical College, Jhansi (U.P)
(Co-Guide)

Certificate

****

*This is to certify that the work entitled **"INTRAVAGINAL MISOPROSTOL VERSUS INTRACERVICAL DINOPROSTONE IN MID-TRIMESTER ABORTION"** which is being submitted as a thesis for **M.S. (Obstetrics and Gynaecology)** examination, 2004 under Bundelkhand University by **Dr. SHIKHA SINGH,** has been carried out in the department of Obstetrics and Gynaecology, M.L.B. Medical College, Jhansi under my direct supervision and guidance. The observations recorded have been checked and verified by me from time to time.*

Dated :

(~~Shri.~~ B.D MATHUR)
M.Sc., D.H.S.,
Associate Professor of
Statistics & Demography,
Department of Obstetrics and Gynaecology
M.L.B. Medical College, Jhansi (U.P)
(Co-Guide)

Acknowledgement

Whenever any piece of work is satisfactorily accomplished it is never the work of one person but a number of people who silently work behind the screen and go unheard of.

My vocabulary falls short of words to convey my profound gratitude and indebtedness to my revered teacher and guide Dr. Usha Agarwal, M.S., Professor of Obstetrics & Gynaecology, M.L.B. Medical College Jhansi under whose expert guidance and supervision I had the privilege to work. Her keen interest, meticulous attention, valuable guidance, concrete and constructive suggestion, constant supervision and encouragement during the persuit of this work made it possible for me to bring this work to the present form.

It is my proud privilege to express my profound thanks to my respected co-guide Dr. Mridula Kapoor, M.S., Professor and Head Department of Obstetrics & Gynaecology, M.L.B. Medical College Jhansi for her able supervision & kind & benevolent disposition. She has been a constant source of inspiration to me during the course of the study.

I wish to express my admiration to my respected co-guide Dr. Sushila Kharkwal, M.D., Associate Professor Department of Obstetrics & Gynaecology, who bestowed upon me knowledge time to time during the study and made it possible to complete this work. I offer my sincere thanks for her constant help, able guidance and tireless efforts.

I take this opportunity to acknowledge most humbly from the inner recess of my heart my indebtness to Dr. Sunita Arora M.S Professor and Dr. Sanjaya Sharma Associate Professor, Department of Obstetrics & Gynecology, whose inspiring benefaction bestowed upon me generously and helped me to carry out this present work.

It is great privilege to express my deep sense of gratitude to Shri. B.D. Mathur, M.Sc, D.H.S., Associate Professor of Statistics & Demography for his valuable suggestion, which enabled me to take over the difficulties during this period.

I am deeply indebted to my esteemed parents for their love, sacrifice, care and inspiration at every moment of my life and also in this important venture.

Certainly the study would not have been possible without active participation of my husband, Dr. Hari Singh who has always been available with invaluable suggestions and unending encouragement especially when it was at the brink of collapse during the course of study. A short note of praise for my darling daughter 'MINI' and sweet son 'SUNNY' for their sweet distraction, which gave me even more inspiration to complete this mammoth task more urgently and efficiently.

This work would not have been in light without the efficient and excellent typing by Mr. Sanjay Sachan. My thanks are due to him.

Finally I thank my study patients whose kind cooperation made this study possible.

Last, but certainly not the least, I pay my sincere prayer to the ALMIGHTY GOD who gave me power, blessings and encouragement to accomplish this task.

JHANSI
DATED :

Shikha Singh
(Dr. Shikha Singh)

CONTENTS

INTRODUCTION

INTRODUCTION

Population explosion is a global problem. Every three seconds, there are two more mouths to feed. More than 74 million individuals are added to world population every year. This problem is particularly very acute in a developing country like India. India adds to it's population every year total population of Australia. Population explosion leads to poverty, illiteracy, unemployment, and epidemic diseases spread easily leading to increased morbidity in the population. So to bring down this birth rate, various family limitation and spacing methods are available free of cost at family welfare centers all over the country. If any method of contraception fails then there is provision for providing facilities for medical termination of pregnancy.

Abortion is the termination of pregnancy by any means before the foetus is sufficiently developed to survive (Williams, 20th edition). The age of viability is usually taken to be 20 wks in developed countries, and 24-28 weeks in developing countries. Since antiquity, the practice of abortion is in existence. Every year, an estimated 40-60 million abortions are performed worldwide, majorities of which are from the developing countries Abortion was legalized in India on broad socio-medical grounds through the medical termination of pregnancy (MTP) Act (act number 34 of 1971), 1971 legalized by the parliament on August 10, 1971, and enforced across the country from April 1, 1972. The objectives of MTP were,

1. Protection of people from quacks.
2. Protection against economic hazards.
3. Protection against health hazards.

According to section 3 (subsection-2) of the act, a pregnancy exceeding 12 weeks but not exceeding 20 weeks requires the opinion of not less than two medical practitioners. Therefore, any induced abortion performed beyond 20 weeks is unprotected by the umbrella of MTP act. It is considered an illegal abortion, unless it is necessary to save maternal life, according to section 5 of the same act. However, there is an appeal from the MTP committee of FOGSI to increase this duration of pregnancy up to at least 22 weeks to cope up with the increased demand of second trimester termination resulting from recent advances in prenatal diagnosis.

It is paradoxical that inspite of the promulgation of medical termination of pregnancy (MTP) act more than 30 years back, a significant portion of these abortions in India, are still performed illegally and are unsafe. This leads to considerable maternal morbidity, mortality and erosion of national health budget.

The most important reason for liberalization of abortion law is high rate of maternal mortality and morbidity due to illegal and unsafe practices. The termination of pregnancy is neither safe nor simple as to advocate abortion on demand. It has been studied that abortion whether spontaneous or induced, always brings with it hazards resulting in maternal morbidity or mortality. The degree varies with the place and method of abortion and necessary skilled help and ancillaries available.

Due to increased awareness of abortion facilities in hospital, more and more women are taking advantage of termination in first trimester of pregnancy. However, a good percentage of women still come for termination in 2^{nd} trimester. In England and Wales only 10.8 percent of all abortions are performed beyond 12 weeks and in US,

second trimester abortions account for 10 percent of all abortions. The number is higher in developing countries like India. Moreover, the tragedy is that even these relatively smaller number of second trimester abortions are responsible for two-thirds of all abortions related major complications and more than half of the maternal deaths associated with abortion. Unmarried girls and rape victims are late presenters due to social stigma. Non-availability and non-awareness of medical facilities at early gestation due to staying in remote areas is also one of the reasons for resorting to mid-trimester abortion. Another group of patients presenting in mid-trimester are females with diagnosed congenitally malformed foetuses. Thus, formulating a cost and time effective and safe mid-trimester abortifacient is the need of hour for most obstetricians.

First trimester abortions are almost universally performed by surgical evaluation. Surgical evaluation is not safe in mid-trimester and various agents tried for inductions of second trimester abortion are not very promising. Unfortunately, there is no consensus of opinion as regards to the best method for termination of second trimester pregnancy.

The available methods for second trimester abortion are –

1. **Gestation between 13-15 weeks**
    - Dilatation and evacuation.
    - Oxytocics.
    - Prostaglandins.
    - Transcervical intra-amniotic instillation of hypertonic saline (20%) or extra-amniotic instillation of 0.1% ethacrydine lactate is used with limited success.

- To allow the pregnancy to continue upto 16 weeks, when the available intra-uterine instillation techniques can be employed.

2. Gestation between 16-20 weeks.

- Intra-amniotic instillation of hypertonic saline (20%) or hypertonic urea (40%) or mannitol.
- Foreign bodies in the form of catheters and laminaria tents.
- Extra-amniotic instillation of 0.1% ethacrydine lactate.
- Oxytocics.
- Prostaglandins.
- Dilatation and evacuation.
- Aspirotomy.
- Hysterotomy.

In modern obstetrics, there are only two classes of drugs which are considered in induction of labour and abortion i.e. oxytocin and prostaglandins. Oxytocin alone has been used in field of obstetrics for induction of abortion & labour very widely, as it is cheap, easily available but has proven ineffective in quite a number of cases and then usually supplemented by surgical induction, may be evacuation of products per vaginum or hysterotomy.

So, we are still in search of a better alternative in which medical induction may be done with no failure and avoid surgical supplementation.

To improve the safety of the abortion procedure and expedite expulsion, prostaglandins are considered to be the best. Prostaglandins are extensively used because of their uterotonic

effects, cervical ripening effect. Prostaglandins are comparatively safe, effective and rapidly metabolized if accidentally pass into general circulation. Until now dinoprostone, a PGE_2 analogue has been the traditional protocol. Recently, newer drugs are under trial in search of a more effective and safer abortifacient and to overcome the obstacles in wide use of previous prostaglandins namely high cost and difficult storage requirements.

Mid-trimester termination can be physically and psychologically traumatic for the patient **(Iles, 1989).** A high degree of patients' involvement is required and can be stressful.

Considering the increased incidence and severity of complications associated with surgical methods of termination and the relative lack of adequately trained personnel for second trimester termination of pregnancy by dilatation and evacuation. The need for an alternative and safe methods was more importantly felt than ever.

Misoprostol is a synthetic prostaglandin analogue (15 deoxy-16-hydroxy methyl PGE_1) that has been approved by the food and drug administration (FDA) to be taken orally for the prevention and treatment of gastric ulcers associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs). It has also become an important drug in obstetrical practice because of its uterotonic and cervical-ripening actions. It is widely being used in combination with mifepristone for medical termination of early pregnancy.

Use and dosage of misoprostal in mid-trimester abortion has not been widely studied. This study was therefore so designed to evaluate efficacy, safety and tolerance of intra vaginal misoprostol compared to traditional intracervical dinoprostone in mid-trimester abortion.

Misoprostol has edge over traditional dinoprostone and has several advantages namely –

(i) Misoprostol is stable at room temperature, requires no refrigeration, needles or syringes for its storage and administration.

(ii) It is cheaper (cost 1.25% of PGE_2 analogue).

(iii) Is easily stored (shelf-life 2 years).

(iv) It is effective both orally and vaginally.

(v) It has no bronchoconstrictive action and has slight bronchodilatory action.

(vi) Can be safely used in hypertensive patients.

(vii) Its application is technically easy as it is put in the vagina and not intra-cervically **(Mundle & Young, 1996).**

(viii) It is readily accessible.

(ix) It has lesser side effects by intra-vaginal route.

If the abortion is legalized on demand, the society must accept some responsibility for whatever follows both to the patients and her surroundings. The stress should be laid on the public of all the risk and complications of termination of pregnancy before term. The many delayed complications, physical as well as emotional should not be neglected and therefore complete long term follow up of patients is obligatory.

AIM OF STUDY

AIMS AND OBJECTIVES

The present study is designed :

1. To evaluate the efficacy, safety and tolerance of intra-vaginal misoprostol compared to the traditional use of intra-cervical dinoprostone in mid-trimester abortion.

2. To formulate a standard dosage schedule for mid-trimester abortions using misoprostol intra-vaginally.

3. To evaluate the side effects of misoprostol (intra-vaginal) compared to dinoprostone (intra-cervical) in the usual abortifacient dosages as used in mid-trimester abortions.

4. To study the population coming for mid trimester abortion as regards to age, parity, socioeconomic status, literacy, gestational age and various other parameters.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Historical review

According to the need of society, laws are usually made to change. Before the change of abortion law (April 1971), there were people who considered it highly immoral to think or talk about abortion, while others felt immense need for liberalization of law for inducing abortions.

Since the beginning of this century, the court and non-government authorities have made efforts of lowering the birth rate. This control of child bearing can be achieved by sterilization and other contraceptive devices. Medical termination of pregnancy also plays important role in curbing the flood of population.

Induction of abortion, either to safeguard the life of a pregnant woman or as a method of limiting the family was practiced by human society since ancient times. When where and by whom was it performed first will never be known.

Various techniques of inducing abortion have been reported. Strong poisons were recommended 5000 years ago in an ancient Chinese manuscript written by emperor **Shen Nung.**

Others suggested strenuous exercises, application of hot ashes to the belly and application of different herbs as well. Among primitive people, almost every tribe had some method of abortion.

Eber's Papyrus discussed method of inducing abortions. Abortifacient elements were dates, onions, and fruits of acanthus or honey, which had to be applied over the vulva.

Greeks had knowledge of both spontaneous as well as induced abortion. **Plato (427-347 BC)** recommended obligatory abortion for every woman who conceived after the age of 40 Years. It was also advocated by **Aristotle** for a woman who already had the prescribed number of children, but it had to be done only before quickening.

In about 130 A.D., **Sonarus** probably the greatest obstetrician and gynaecologist of Rome of Mat era, wrote a text on diseases of women in which he commented that it was easier to induce abortion in 3rd month but that endometritis and convulsions (tetanic) may occur as complications.

In 13th century, English jurist **Breaton** framed rules of the common law that killing the foetus after quickening was murder and before quickening it was crime. It was in 1929 that the Great Britain legalized abortion when mother's life was endangered. During last 50 years there has been changes performed in abortion laws in various countries of the world.

Abortion in India

The increased mortality and morbidity due to the illegal abortion was a matter of concern to everybody in medical field. MTP was legalized in India with two main reasons in mind. Firstly, as a population control measure as population control could not be achieved satisfactorily by the various contraceptive methods either due to individual's method failure or due to non-adoptation by the ignorant and uneducated masses.

The second objective was to transfer large number of criminal abortions with all their complications from the untrained quacks, to the safe hands of skilled and specialized gynaecologist.

Gynaecologist entrusted with this responsibility looked at the problem with four aspects-

1. The method employed should be safe for mother.
2. The technique used should be easy.
3. The procedure should not involve prolonged hospital stay, thereby accelerating rate of turnover per bed.
4. Lastly, the method should be cheap.

The method of termination of pregnancy from 12^{th} week onwards is a problem of obstetricians even today. The chief aim is physiological delivery of the foetus with safety to the mother.

Various methods tried for mid- trimester abortion are –

A. Surgical abortion :

1. Dilation and Evacuation

In USA and in non-NHS sector in UK, dilatation and evacuation is considered as preferred method for termination of second trimester pregnancy. This method is faster, carries no risk of live birth, is more compassionate in terms of women and can be performed on a out patient basis. A greater degree of skill is required to perform this procedure, a safe and effective method only in the hands of those who are trained and skilled in the technique. Serious complications like cervical laceration, uterine perforation and bowel injury are a distinct possibility even in the hands of expert. Although D/E is reported to be the safest method of second trimester abortion, beyond 16 weeks this procedure is taught infrequently **(Auntry, AM et al, 2002).**

2. Aspirotomy

This is a combination of vacuum aspiration of liquor followed by embryotomy and removal of the products of conception under para-cervical block. Although not a mandatory pre requisite, this procedure can be better performed under ultrasound guidance. In spite of the claim of almost similar results and complications like D/E, the method never became popular, possibly because of significantly high incidence of anticipated complications and the need for development of expertise and skill in the procedure.

3. Hysterotomy

Effective non-surgical methods have made surgical procedures, particularly the traditional hysterotomy almost obsolete and largely discredited. Now the only role of hysterotomy is in rare cases of failure following induction of abortion.

B. Medical Abortion

Medical abortion is ideally an attempt to stimulate uterine contraction and initiate cervical dilatation with an aim of complete expulsion of products of conception so as to mimic a mini-labour. Considering the increased incidence and severity of complications associated with surgical methods of termination and the relative lack of adequate trained personnel for second trimester termination of pregnancy by dilatation and evacuation, the need for an alternative and safe method was more importantly felt than ever. The scope of training for development of skill, the technique of dilatation and evacuation, amongst the junior residents is gradually becoming far from reality and is now regarded as a lost art. When morphometric evaluation of the foetus is required, as in cases of second trimester termination due to genetic abnormality, medical abortion is a better option. Moreover, the protocol for medical abortion does not require

any special training and can be easily performed by the junior residents in a hospital with appropriate infra-structural back up.

1. Cervical tents

Tents enjoyed a long history of varying popularity. It decreases cervical resistance to forceful dilatation. Cervical ripening prior to surgical termination of pregnancy allows a greater cervical dilatation to be safely, effectively and confidently achieved thereby minimizing the complications.

The classical tents (laminaria) were derived from natural materials. Synthetic tents like Dilapan and Lamicel are also now available. Laminaria should be left in situ for 4-12 hours, lamicel for 4 hours and dilapan for 2-4 hours. Exceeding these limits achieves no further dilatation and the risk of sepsis, dumb swelling and entrapment increases.

Although never considered as a primary agent, tents are useful adjuncts to other methods for termination of second trimester pregnancy. The insertion of laminaria tent requires trained personnel. In addition to potential complications such as in rauterine displacement and perforation of the cervix, tents also cause discomfort to the patient.

2. Balloon Insertion

Introducing the foley's catheter through the cervix, inflating the balloon with 30cc sterile saline and finally pulling the catheter downward until the balloon is engaged by the cervical internal os is an inexpensive and effective way of second trimester termination of pregnancy. Oxytocin augmentation was used with the expulsion of catheter or with the initiation of uterine contraction, when necessary.

The procedure is considered as failure when there is no effective uterine contraction or cervical dilatation within 48 hours. The main drawback of the balloon insertion is the discomfort caused by the strapping of the catheter to the patients inner thigh firmly that provides traction to the cervix.

3. Intra Amniotic Hypertonic Saline

For procuring second trimester termination, intra-amniotic instillation of hypertonic saline (20%) was extensively used in Japan from 1946 to 1952. The results were satisfactory with an average induction-abortion interval of 32 hours and a success rate of almost 80% within 48 hours. However, the complication rates were also high, the commonest being haemorrhage due to incomplete abortion and infection. The other noted complications were cervical tear, hypernatremia (rarely severe), and necrosis of myometrium and rarely coagulopathy. More importantly, the unacceptably high maternal mortality has ultimately become responsible for its gradual decline in use.

4. Ethacridine Lactate

Ethacridine lactate was first used by **Miranov** in Russia in 1950 for second trimester pregnancy termination. Trans-cervical extra-ovular instillation of this acridine dye was found to be an inexpensive, safe and effective method by various authors. Extra-amniotic route was found to be more effective as compared to intra-amniotic route. Administration of various abortifacients through extra-amniotic route dates back to 1846, although **Manabe** popularized it. This route is devoid of the complications associated with intra-amniotic route and can safely and effectively be employed between 12-14 weeks of pregnancy (so called grey zone of pregnancy). The drawback of this method has been reported to be the

long induction-abortion interval (23-42 hours) and the need for augmentation with oxytocin in majority of cases. However, simultaneous use of different drugs or devices having synergistic effect on uterine stimulation may reduce induction abortion interval and also increase success rate-

5. Urea

Intra-amniotic instillation of 150-200 ml of 40-60% Urea, an inert substance, has been observed to be effective in procuring second trimester termination. As compared to hypertonic saline urea is less toxic to maternal tissue. The success rate is also lower than hypertonic saline. However, addition of adjuvants like intra-amniotic $PGF_2\alpha$ or introduction of intra-cervical tents helps to improve the success rate.

6. Oxytocin

Caldeyro Barcia et al found that the oxytocin dose required to produce 120 montevidea units of uterine activity is eight-fold higher at 20 weeks of gestation than at 38 weeks. This weak uterine response to oxytocin at early weeks of gestation is the greatest obstacle of using oxytocin infusion for achieving second trimester termination of pregnancy. Clinical and biochemical observations suggest that a concentrated oxytocin infusion protocol may be effective. Highly concentrated oxytocin solution (300 IU / 500 cc oxytocin over three hours) may lead to water intoxication. However, standard oxytocin infusion protocol is commonly used as an adjunctive to other protocol with an aim to reduce the induction-abortion interval and also to increase the chance of completeness of abortion.

Newer drugs in use

7. Mifepristone

Progesterone is central to the maintenance of pregnancy and is thus the ideal target for fertility regulation. Mifepristone, a receptor blocker, is usually given as pre treatment, prior to prostaglandin administration in mid-trimester termination of pregnancy.

Pre treatment with mifepristone required significantly fewer gemeprost pessarises to induce abortion and experienced significantly less pain than the women who received placebo and this combined regimen is also associated with fewer gastrointestinal side effects **(Rodger MW et al, 1990)** pre-treatment with oral mifepristone (100mg daily for two days) optimizes the outcome of vaginal misoprostol for mid-trimester termination, **(Cheng L et al, 1999).**

The combination of oral mifepristone 200 mg single dose followed by vaginally and orally administered misoprostol provides noninvasive and effective regimen for second trimester termination of pregnancy **(Ashok PW et al, 1999).**

8. Trilostane

Trilostane is a 3∝-hydroxysteroid dehydrogenase inhibitor, which reduces progesterone production from its precursor pregnenolone. As a pretreatment, prior to misoprostol administration trilostane, was evaluated in second trimester termination. Trilostane is an effected pretreatment agent by reducing the induction to abortion interval in mid trimester termination **(Roux PA et al, 2002).**

9. Prostaglandins

The uterine stimulation and cervical ripening property of the prostaglandins was successfully utilized for termination of second

trimester pregnancy since last four decades. All possible routes were tried-intravenous, intramuscular, intra-amniotic, extra-amniotic and vaginal.

Currently used products are analogous of PGE_1 (gemeprost, misoprostol).

a **Dinoprostone** (PGE_2 gel) is also an effective method of cervical ripening when used intra cervically. But retained placenta in 2% was a major complication and also has severe gastrointestinal side effects.

b **Gemeprost** is available as vaginal pessary (1mg). Intravaginal route is used and repeated at a varying interval of three to six hours. Gemeprost can be used synergistically with pre treatment with miferpristone.

c **Misoprostol** synthetic PGE, analgesic initiates cervical dilatation and stimulates an increase in intensity and frequency of uterine contraction. It discussed in detail later on.

Prostaglandins

Prostaglandins are naturally occurring compounds found in body secretions and are readily released.

Historical survey

Prostaglandins were first discovered in seminal fluid by **Kurzrok** and **Liebin** (1930), who noted that human uterus undergoes strong uterine contractions on instillation of fresh human semen.

Von Euler coined the name prostaglandin in 1935, as it was thought to be secreted from the prostate but it was misnomer as it was the secretion which has been isolated by **Bergstone** and **Sjovall** in crystalline form from the sheep's seminal vesicle. The compound was not paid much attention until the II^{nd} world war.

Prostaglandins were used for the first time in 1963 by **Karim** and associates for induction of abortion. Since then a large number of trials have been carried out in many countries on induction of labour and abortion. Prostaglandins have been found to be very effective at any stage of pregnancy, so it is found to be very useful for missed abortion, intrauterine deaths and hydatiform mole **(Roth Bkandel and Karim Filsh, 1970).**

Prostaglandins are effective in first as well as in IInd trimester abortion. Various routes have been tried to evaluate the efficacy and to lower the side effects. First of all, intravenous $PGF_2\alpha$ infusion was tried. This route was associated with unacceptable side effects like hypotension, nausea, vomiting and thrombophlebitis.

Next intrauterine route was tried, with the aim to localize the site of action and reduce the systemic side intra-amniotic routes were tried with high efficacy and less side effects but required intra-uterine manipulation and repeated administration involved potential risk of sepsis. To get rid of intra-uterine manipulation, PGF_2 was tried by intra-muscular and intra-vaginal routes.

Distribution of prostaglandins in human reproductive organs and fluid

Recent and more definite studies have shown that the distribution of prostaglandins is not restricted to male accessory

glands or their secretions as reported earlier, but prostaglandins have universal distribution in the female reproductive organs and fluid also. With increasing and ongoing researches, evidence has accumulated that prostaglandins are active throughout the reproductive system.

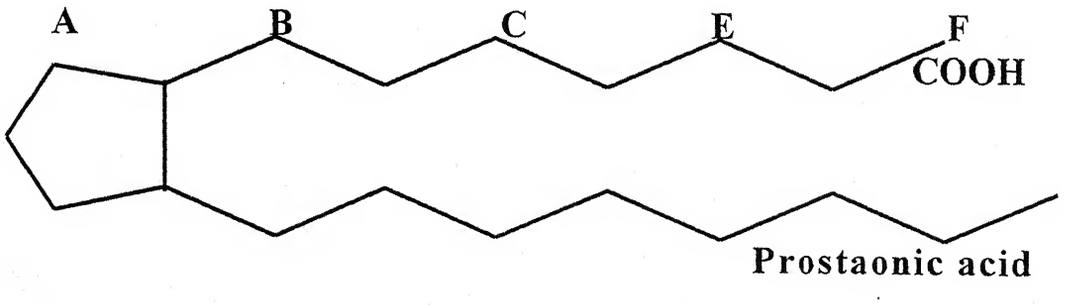
By the late 1970's, prostaglandins were known to be involved in hypothalamic and pituitary hormone release, ovulation, development of corpus luteum, uterine contractions in labour, spontaneous abortion ejaculations and sperm transport.

Location, structure and purification

The isolation of prostaglandin E_2 and $F_2\alpha$ in pure crystalline form from the sheep vesicular gland was reported in 1957 by **Berystrom** and **Sjovall.** With the elucidation of the structure of primary prostaglandin and the total synthesis by **E.J. Corey et al. Haward** (1969) and **UP John company**, became universal. The ultramicro analysis proved that they were unsaturated hydroxy fatty acid has empirical formula $C_{20}H_{34}O_5$ and $C_{20}H_{36}O_5$ respectively. 13 different compounds were isolated, all derivative of parent substance prostanoic acid containing 20 carbon atoms.

Prostaglandin are divided into five types based upon the chemical functioning in the ring structure called cyclopentane and two side chains and are named as F,E,A,B and C.

Structure



Prostaonic acid

Prostaglandin are again grouped into mono, bis or tri unsaturated classes according to the number of carbon to carbon double bonds in the side chains which is sited as 1,2,3 in the subscripts e.g. PGF_1, PGF_2 and PGF_3. They are divided into stereo isomer and are substituted alpha or beta e.g. PGF_2 alpha.

The extracts of sheep seminal vesicle yield very little amount of prostaglandin and was very expensive, so chemical synthesis by **E.J. Corey** has provided very inexpensive prostaglandins in large amounts.

Occurrence

Prostaglandins are found in all mammalian tissues & body fluids e.g. seminal fluid, lungs, kidney, brain and reproductive system **(Anderson, 1974).** The concentration of prostaglandins is 100 μg/ml in seminal fluid, while in other tissue it is less than 11 μg/gm.

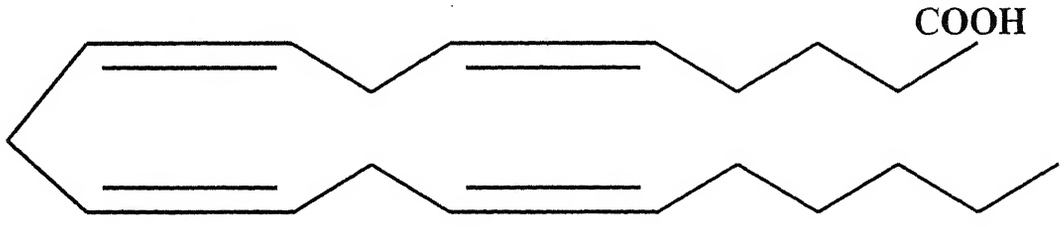
Biosynthesis and Metabolism

The complex enzymic system which takes part in synthesis of prostaglandins is present in every mammalian tissue. Capability of synthesis is different in different tissue e.g. in seminal vesicle it is 75%, 10-20% in lungs and kidney, 3% in gut and less than 1% in spleen and aorta. They are synthesized from essential fatty acids. Among them arachidonic fatty acid is the most important. First step in the bio conversion of arachidonic acid to prostaglandins (PGF_2 and $PGF_2\alpha$), prostacyclins (PGI_2) and thromboxane ($T\alpha A_2$) is the formation of cyclic endoperoxides, prostaglandin G and H. The enzyme responsible for the conversion of AA to PGH_2 is known as fatty acid cyclo-oxygenase or prostaglandin edoperoxide synthetase or PGH synthetase.

NSAIDS like aspirin and indomethacin can inhibit the action of cyclo-oxygenase thereby inhabiting the formation of prostaglandins. Depending on the tissue, the endoperoxidases are further converted non-enzymatically into PGE_2, $PGF_2\alpha$, PGI_2 and $T\alpha A2$ **(Sammelsson et al. 1975; Sammelsson et al. 1978).** These conversions are extremely rapid and once the biosynthesis is initiated, it is completed within the few minutes in invitro system **(Hamberg et al. 1975, Christensen** and **Green 1983).**

Structure

Arachidonic acid



Metabolism

Natural prostaglandins are metabolized rapidly by beta-oxidation which is the major route and also by dehydrogenases. The enzymes involved in the initial conversion are found in the lungs, liver and kidney **(Auggard, Larsson and Sammelsson, 1971).**

After intravenous administration of PGF_2, the drug disappear very rapidly during the first ten minutes then reaches a steady low level in first hour, excreted completely in ten hours. Total recovery is 60% by excretion i.e. 40% from the urine and 20% from the urine.

Physiology and pharmacology

Prostaglandins cause contraction of all smooth muscles. Response could be modified with change of ionic composition of medium, hormones and blocking agents.

Mechanism of action

The mechanism seems to be by oxidative metabolism. Probably it causes membrane depolarization and release of bound calcium. Action of PGE and PGF alpha are quantitatively similar but different receptors may be involved.

Parturition : Although a controversy still exists about the factors responsible for the initiation of labour, the fact that the prostaglandins are involved in the physiology of labour as well as in the patho-physiology of spontaneous abortion and premature abortion and premature labour is based on the following observation made by various workers.

- Stimulatory effect of prostaglandins on the pregnant uterus.
- Cervical priming.
- Raised levels of prostaglandins and their amniotic fluid during labour and spontaneous abortion.
- Inhibitory effects of prostaglandin antagonist and synthetase inhibitors on the uterine contractions.

Effect on human uterus :

Non pregnant uterus

In vitro studies : The PGE compounds generally inhibits, while PGF compounds stimulate the non-pregnant myometrium. The sensitivity is more to E compounds at ovulation, while to F compound, it is more at premenstrual period.

Non pregnant cervix

PGF2 causes marked relaxation, while F2 alpha results are unpredictable inhibition, contraction as well as no effect has been seen.

Pregnant uterus

The stimulatory effect of naturally occurring prostaglandins on the human myometrial strips obtained from one of the uterus in first and second trimester of pregnancy was first demonstrated by **Bygdeman,** 1964. PGF compounds are always stimulatory during pregnancy and sensitivity of myometrium is much higher than non pregnant.

In Vivo studies

The effect of PGE and PGF on pregnant uterus is always stimulatory **(Roth Brandal et al, 1970; Bygdeman et al, 1970 and Karim 1971).**

The sensitivity increases as term approaches. The stimulatory action is seen by different routes like intravenous, intramuscular, oral, vaginal, intrauterine (extra and intra amniotic).

However, the stimulatory response observed with the intra-amniotic PGF2 alpha was found to be different from the response obtained with intra-amniotic **15 (S) 15 methyl PGF_2 alpha (Wilquist et al. 73).** He summarized the stimulatory effect with an analogue as slower to develop, reaching maximum after 4-hours but subsequently maintained at this level throughout the 24 hours of observation. In comparison, the intra amniotic injection of $PGF_2 \alpha$ caused a rapid uterine response which reached a maximum within 2-3 hours and then ablated progressively. The exact mechanism of action is still not

known. According to **Carsten** (1972), there are many PG receptors on the sarcoplasmic reticulum of the myometrium (intracellular membrane), which are responsible for conducting the signals to the myometrial fibres to contract and for initiating the contraction itself. PGE_2 and PGF_2 alpha cause the membrane to release the bound calcium into the cell fluid, these calcium ions in turn trigger off the contraction of the muscle fibres. The other possibility is that it acts indirectly through the release of oxytocin. **Givespic et al**. 1972; have shown an increase of oxytocin levels in prostaglandin induced labour, and initiated that the increase is due to direct effect of prostaglandin on the pituitary. **Caspo** and **Pulkkinen (1979)** have suggested that the constriction of uterine and placental blood vessels is the first event which leads to the reduction in prostaglandin supply, thus making the myometrium receptive to prostaglandins.

Effect on Pregnant Cervix in vivo

The second major action of prostaglandin is on the cervix. It softens and dilates the cervix, commonly referred to as cervical priming or ripening. Prostaglandins, particularly PGE_2 that especially alter the structure of the connective tissue of the cervix and make it soft and dilated.

Prostaglandins in maternal circulation and amniotic fluid

Karim in 1986 demonstrated an increase in concentration during labour. The peak of PGF2 alpha was observed in the plasma 15 to 45 seconds after the peak of uterine contraction **(Sharma et al, 1973)** he reported a significantly higher concentration of PGF2 alpha in the umbilical vein of babies born vaginally as compared to those delivered by elective caesarean section.

Amniotic fluid is another resource from where a high concentration of prostaglandins have been reported during labour by many workers. Karim (1966) and Devlin (1967) were first to identify PGF2 alpha in amniotic fluid, during pregnancy and labour, and found it in higher concentration at the time of active labour. This rise in amniotic PGF2 alpha level during labour was not confined to the full term pregnancy but was observed during spontaneous abortion also. (Karim and Hiller, 1970).

Inhibitory effect of prostaglandin antagonist and synthesis inhibitors on uterine contractions

The satisfactory inhibition of uterine contraction with a prostaglandin antagonist or inhibitors of their synthesis, in the case of prostaglandins are involved in the physiology of labour.

The use of Ethyl alcohol to inhibit uterine activity in women with threatened abortion and premature labour was demonstrated by Fuchs et al (1957). The same authors showed that the administration of ethyl alcohol does not affect the uterine activity induced by oxytocin. Lewis and Schulman (1973) reported that aspirin (an inhibitor of prostaglandin synthesis) treatment in normal human pregnancy prolongs gestation and increases the duration of labour.

Lactation and prostaglandins

The physiological and pharmacological involvement of prostaglandin in lactation is not clear. The response of the human mammary tissue to prostaglandin was first studied by Cobo et al in 1974. They observed milk ejection property, both with PGF_2 alpha when administered by single intravenous injection as with the equiactive amount of oxytocin. However, a latent period of 30-90 seconds was noted with PGF2 alpha before the response and the same

was two to four times greater than that of oxytocin. The exact mechanism of action of prostaglandin in increasing mammary pressure is not clear. Probably the prostaglandin acts indirectly either by oxytocin release or due to a metabolite of prostaglandin. The latent period observed in their study favours the oxytocin release theory while the long duration goes in favour of the metabolite theory.

Indirect evidence for the involvement of prostaglandin in lactation was shown by **Shearman et al. (1972)** who showed that almost all the patients experienced lactation after the intra-amniotic or extra-amniotic injection of prostaglandin for the termination of second trimester pregnancy.

Nasi et al. (1979) have reported inhibition of lactation by oral tablets of PGF_2 the physiological mechanism involved in the inhibition of lactation is not known.

Fallopian tubes

PGE causes relaxation of tube while PGF_2 contracted all parts of the tube.

Ovary

In animals prostaglandin acts as leuteolytic factor causing regression of corpus luteum and onset of menstruation regularly. In human beings prostaglandins have no effect on corpus **luteum (Karim 75, Anderson 74, Duchhoelter et al. 78).**

Menstruation

Endometrium produces both PGE and PGF_2 alpha and their level rise during luteal phase. These are also responsible for endometrial shedding, vomiting and pain in lower abdomen during menstruation.

Endogenous prostaglandin production decreases if progesterone, aspirin or indomethacin were given. **(Helbert 1970 Juvier, 1974).**

Clinical application of Prostaglandins in obstetrics

1. Prostaglandins as abortifacient

Prostaglandins were first used for induction of labour in 1968. it was based on the fact that prostaglandin levels were such to be increased in maternal blood and amniotic fluid during labour and during cervical dilatation in cases of abortion. The abortifacient activity of prostaglandin is based upon the fact that it stimulates uterus at any gestational age.

The various hypothesis are :

i. **Direct myometrial stimulation :** Prostaglandin cause contraction and relaxation of uterus, due to increasing contraction of uterus, conceptus gets dislodged and results in abortion **(Bergstrom et al 1971).**

ii. **Effect on foeto-placental unit :** This is most widely accepted theory by **Coceani et al 1972**. According to this theory prostaglandin first induces uterine contraction. Sustained uterine contraction causes decreased blood supply to placenta and throphoblast. This reduction in uterine blood flow causes suppression of foeto-placental endocrine function i.e. HCG levels become low. This in turn reduces corpus luteum activity and decreases progesterone levels. It has double fold effect. It reduces myometrial threshold for contractility and also results in increased endogenous prostaglandin synthesis. The overall effect is increased cyclic uterine activity, which results in abortion **(Canter et al, 1971).**

2. **Use of Prostaglandin in abnormal pregnancy :** Various investigators have used prostaglandins for the termination of missed abortion, hydatiform mole, intrauterine foetal death and anencephalic pregnancy.

3. **Induction of labour :** Prostaglandins are being used extensively in induction or augmentation of labour either spontaneous labour or induced.

4. **Post partum haemorrhage :** Prostaglandins have been found to be effective in controlling postpartum uterine haemorrage when administered by different routes. Local administration directly into the uterine musculature trans abdominally or transvaginally, resulted in the dramatic reduction in rate of bleeding **(Takagi et al, 1976; George et al, 1983).**

5. **Dysmenorrhoea and other uterine pathology :** From the result of the studies one may conclude that prostaglandin is one of the causative factors. In the aetiology of primary dysmenorrhoea. **Pickles & Hall (1963)** demonstrated a higher than normal amount of PGF2 α in the menstrual fluid of dysmenoerhic women. These levels were reduced after aspirin and indomethacin administration.

6. **Intra uterine contraceptive devices :** The possibility of involvement of prostaglandin in the anti-fertility action if IUCD is evaluated by some investigators.

7. **Preoperative cervical dilatation :** The use of prostaglandin analogues for the dilatation of the cervix gives a better success rate than the usage of tents or other procedures.

Side effects

Prostaglandins have numerous side effects but none of them is life threatening and they disappear very rapidly on withdrawing the drug. These side effects are due to action of prostaglandins on various tissues of the body.

1. **Gastro-intestinal tract** : Vomiting, diarrhoea and abdominal pain are the most common side effects with prostaglandins. The cause of diarrhoea is enteropooling i.e. accumulation of fluid in small bowel, the cause of this pooling is :

    - Inhibition of reaabsorption of fluid from intestinal lumen by prostaglandins.
    - Out pouring of fluid from blood into lumen.

    The degree of enteropooling is dependent upon the dose of prostaglandin. The fluid then moves into large intestine and gets mixed with normally formed stools which are expelled out. Thus action is just like Cholera exotoxin (Robert et al, 1976). Lomitil controls diarrhea partially and loperamide has slightly higher therapeutic value. it acts by inhibiting peristalsis by interfering with cholinergic and non-cholinergic mechanism.

    Vomiting is due to local effect on intestine and can be controlled by prochlorperazine. Abdominal pain is due to contraction of intestinal muscles. Prostaglandins of F series have more Git side effects.

2. **Uterine pain** : The cause of uterine pain is rise in uterine tonus, the base line tonus becomes 20-25 mmHg which gives rise to continuous pain. Pethidine is presumed to be effective analgesic

for this, without interfering with the abortifacient activity, but is rarely required.

3. **Fever** : The cause of fever is action on temperature regulating mechanism probably at hypothalamic level, the temperature comes down after abortion. PGE series have more specific pyrexial action than PGF series.

4. **Respiratory side effects** : Prostaglandins sometimes produce brochospasm, dyspnoea and respiratory difficulty. The cause is stimulation of respiratory smooth muscles. PGF series have been found to be vasoconstrictors (**Zurior et al, 1974**) while PGE series has vasodilator action. So, PGF series give rise to respiratory difficulty on I.V. infusion while PGE series may be used to cure the asthmatic patients (**Zurier et al, 1974**).

5. **Cardiovascular side effects** : **Fishburn et al. (1972)** has reported no change in cardiac output, heart rate or central venous pressure even with large doses of PGF_2 alpha by I.V. infusion. **Lee et al, (1974)** has reported that PGF_2 infuses causes fall in blood pressure especially in diastolic blood pressure. With large intravenous infusion flushing of face, headache, flashes of light, dizziness etc have been reported which are due to relaxant effect of prostaglandin on vascular smooth muscle.

6. **Effect on blood coagulability** : Prostaglandin cause a decrease in haematocrit value but all other factors are increased. It causes a significant increase in platelets, fibrinogen, factor V and VIII and fibrinolytic inhibitors (**Philips et al, 1974**) this is in marked contrast to saline infusion when used for abortion which causes decrease of all these levels. The increase in clotting factor is due to mild inflammatory process produced by prostaglandins.

7. **Effect on central nervous system** : There is small risk of generalized convulsion in normal patients and greater risk in persons with previous history of seizure **(Sheerman et al, 1972).**

8. **Lactation** : **Sheerman et al, (1972)** has reported a clearly high incidence of lactation following mid-trimester abortion by Prostaglandin.

Complications

Complications of Prostaglandins are not many but few may be very serious if not attended to in time.

1. **Haemorrhage** : This is most common complication. **Duenhoetter et al (1975)** has reported fall in Hb in 13.1% cases with intra-amniotic administration. **Laursen and Wilson (1975)** have described the blood loss between 75-150 ml in patients induced by intramuscular route.

2. **Infection** : **Duenhoelter et al, (1975)** has described the incidence requiring antibiotic therapy as 14.8% following intra-amniotic route. **Laursen and Wilson (1975)** have reported fever in 20% following induction by intramuscular route.

   Karim and Wiiquist (1973) have reported that only 5% cases have fever following intramuscular route, and cause of pyrexia by premature rupture of membrane.

3. **Uterine and cervical rupture** : Rupture of cervix are rare and serious complications as they interfere in future child bearing. Cervical rupture leads to future premature deliveries, while uterine rupture necessitates hysterectomy.

   Following intramuscular injection of PGF_2 alpha, **Hernique et al, (1977)** has reported cervical laceration in 2 out

of 63 patients. The cause was cervical dystocia. Hernique has also described ballooning of cervix in 2 patients without cervical dilatation. The cause of these tear is not very well understood. The tear had been mainly transverse and in posterior cervical lip. The cause could be either active cervical contraction or a very rapid onset of strong uterine contraction due to patient's cervix not getting time to dilate. This complication is mainly seen in young primigravid patients. To avoid this complication cervix should be dilated prior to myometrial contraction.

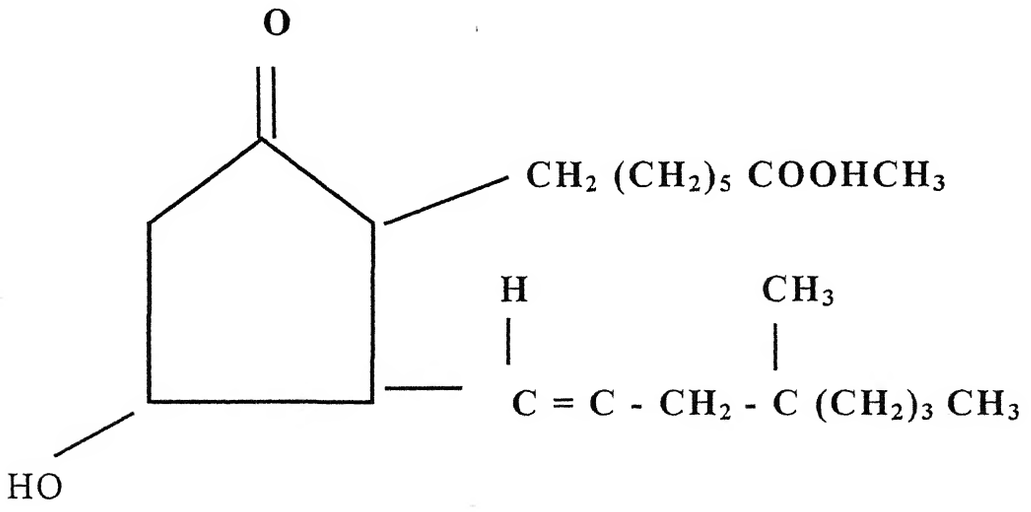
4. **Failure to abort** : Failure to abort is due to lack of sensitivity of uterus to Prostaglandins. **Lauersen (1976)** reported that when patient fails to abort she should be checked for uterine malformation and fibromyoma.

Prostaglandins are involved in every stage of human reproduction. Ever since von Euller gave the name 'Prostaglandin' to a substance found in the extracts and secretions from the human prostate and seminal vesicles there have been nearly yearly developments in the search of newer Prostaglandins with better efficacy and tolerance.

In 1968 **Karim** introduced Prostaglandin infusion (PGF_2) for induction of labour. In 1986 PGE_2 cervical gel (Dinoprostone) was introduced. The development of mifepristone began in 1980. In 1988 France was the first country, which use mifepristone in combination with Prostaglandin analogues.

In this series of researches Misoprostol was introduced by **El-Refaey et al in 1995. Zeiman et al** compared the absorption kinetics of misoprostol after oral and vaginal administration. In 1999 **Lehavi et al** first reported its intravaginal use.

The new synthetic analogue of PGE_1 (Alprostadil) is misoprostol. Naturally occurring PGE_1 is not orally sustainable as it is unstable in acid media, and also not suitable for parenteral use because of its rapid degradation in the blood. Synthetic PGE_1 analogue has been produced by bringing about an alteration in the chemical structure of this naturally occurring compound, thereby making it orally stable and clinically useful. The chemical formula of misoprostol is $C_{22}H_{38}O_5$ or (±) methyl (13E)-11, 16 dihydroxy-16methyl-9-oxo-prost-13-enolate.by relocating the 15-hydroxy group to the adjacent 16 position and addition of a methyl group to carbon 16, misoprostol has developed from PGE_1.



Chemical structure of misoprostol

Addition of a methyl group to the carbon-16 position, C-16 hydroxy group is less susceptible to the action of 15-dehydrogenase enzyme that inactivates natural PGE_1 **(Collins PW)** the carbon-15 position of the hydroxyl group has been shifted to the carbon-16 and this reduces the side effects, misoprostol contains approximately equal amounts of the two diasteromers presented below with their

enantiomers indicated by (±). Misoprostol is water soluble, viscous liquid.

Pharmacodynamics and pharmacokinetics

Misoprostol is manufactured as an oral preparation in 100μg and 200μg tablets. These tablets can be used orally, vaginally and rectally. After oral administration, misoprostol is rapidly absorbed and converted to it's pharmacologically active metabolite, misoprostol acid, and is further metabolized by fatty acid oxidizing system present in numerous tissues of the body. The serum protein binding of misoprostol acid is less than 90% and is concentration independent in the therapeutic range. The bioavailability of misoprostol is decreased by concomitant ingestion of food or antacids. Misoprostol is primarily metabolized in the liver, and less than 1% of its active metabolite is excreted in urine. Patients with hepatic disease should receive a decreased dose, whereas dose adjustment is unnecessary for patients with renal insufficiency and in those who require dialysis. Misoprostol has no known drug interactions and does not induce the hepatic cytochrome P-450 enzyme system. Most nonsteroidal anti-inflammatory drugs do not produce any change in their kinetics when used with misoprostol, except clinically non-significant 20% decrease of aspirin activities. Similarly no drug interaction has been noted with antipyrine, propranolal and diazepam.

Absorption kinetics as studied by **Zieman et al, (1997)** proved that vaginal application is superior to oral administration. Vaginal application has the advantage of reducing gastrointestinal side effects and exerts profound effects on reproductive tract, thereby this route has been used extensibly in different clinical conditions related to obstetrics and gynecology.

After application in the posterior fornix, plasma concentration reaches peak by one to two hour and then slowly declines unlike oral absorption. Slower increase and lower peak plasma concentration of misoprostol is noted in vaginal application when compared to oral application but overall exposure to drug is increased following vaginal application.

Following oral administration peak level is reached between 12.5 and 60 minutes and falls steeply by 120 minutes. In contrast, plasma concentration of the drug in women receiving vaginal dose, rises gradually and reaches maximum levels between 60 – 120 minutes. Plasma concentration declines slowly to an average of 61% of the peak level at 240 minutes after vaginal application and the bioavailability of the drug is 3 times higher than that after oral administration probably due to its by-passing the gastrointestinal and hepatic metabolism.

In vivo studies have shown that after oral and vaginal administration of the drug, intrauterine pressure begins to increase by 8 minutes and reached maximum by 25 and 46 minutes respectively. Uterine contraction exerted by this drug also differs when applied by different routes. After oral administration uterine contraction peaks up by next one hour and then attains plateau whereas uterine contraction rises continuously for next four hours after vaginal application, maximum uterine contractility was significantly higher after vaginal administration.

Posology

Unless given in a high dose, this drug does not produce any deleterious adverse effects. Though toxic dose of this drug is yet to be

determined, however, cumulative dose upto 2200μg has been tried in varying doses from as low as 25 mg to 800 mg either alone or in combination with agents to achieve clinical efficacy.

Adverse effects

Like other prostaglandins misoprostol also has common gastrointestinal adverse effects such as nausea, vomiting, diarrhea, abdominal pain, dyspepsia, flatulence and constipation (rarely). Other dose dependent side effects are pyrexia, chills, shivering and headache. Skin rashes and dizziness have been infrequently reported. Myocardial infarction and bronchosasm has not been reported yet with misoprostol which are not uncommon with prostagland $F_2\alpha$ and E_2. Very high doses like 600μg taken orally (with trifluoperzine) to terminate pregnancy has been reported with abortion, hyperthermia, rhabdomyolysis, hypoxemia. Gynaecological disorders like spotting, cramps, hypermenorroea, dysmenorrhoea and post menopausal bleeding have been reported in clinical trials in a small number of patients. Insignificant side effects involving different systems has been reported in clinical trials.

Safety profile

Though the toxic dose in humans has not yet been determined, acute toxic effects has been reported in animal studies in the form of diarroea, gastrointestinal lesions, focal cardiac necrosis, hepatic/renal tubular necrosis, testicular atrophy, respiratory difficulties and depression of central nervous system. Over dose has been clinically manifested by sedation, tremor, convulsion, dyspnoea abdominal pain, fever, dirreoea, palpitation, hypotension or bradycardia and should be treated with supportive therapy. It is not yet known if misoprostol acid is dialyzable. However, because misoprostol is metabolized like a

fatty acid, it is unlikely that dialysis would be appropriate treatment of overdose.

Misoprostol does not produce any significant effects on serum levels of prolactin, gonadotropins, thyroid stimulating hormone, growth hormone, thyroxine (somatostatin, gastrin, vasoactive intestinal polypeptide and motilin), (creatinine or uric acid. Gastric emptying, immunologic competence, platelet aggregation, pulmonary function or the cardiovascular systems are not modified by recommended doses.

Teratogenicity

Moebius' syndrome (congenital facial paralysis) and limb defects have been reported occasionally in infants of women who ingested misoprosal in 1st trimester in an unsuccessful attempt to induce abortion. Among women who have delivered children affected with moebius' syndrome, the likelihood of exposure to misoprostol in Ist trimester is very high. The absolute risk of this syndrome among all women exposed to this drug in the Ist trimester is possibly low. Localized ischemia in the placental bed and vascular disruption in the embryo are postulated as the operational mechanism for causing the congenital anomalies.

In a recent case control study, malformations like transverse limb defects ring-shaped constriction of the extremities, arthroryposis, hydrocephalus, holoprosencephaly and extrophy of bladder, but not moebius' syndrome has been reported in infants.

Mechanism of action

Misoprostol is a synthetic PGE_1 analogue. It has actions mainly on gastrointestinal tract and uterus. Like endogenous PGE_1,

misoprostol exerts a protective effect on the gastrointestinal mucosa by increasing mucus and bicarbonate ion secretion and by increasing mucosal blood flow. In addition, misoprostol inhibits acid secretion. Misoprostol acts locally on the parietal cells to decrease acid secretion. It also exhibits local mucosal protection by supplying an exogenous source of prostaglandins. The principal active metabolite (misoprostol acid) is rapidly metabolized and absorbed following oral administration. Thus, it provides protection against the erosive effects of NSAIDS.

In addition, misoprostol is also myometrial stimulant, which binds to both E_2 and E_3 prostanoid receptors. It also has cervical ripening effects. Its active plasma metabolite is misoprostol acid. It is rapidly absorbed after oral, vaginal and rectal administration. With oral, administration the half life is less than 30 minutes, and peak level is at 15 minutes. After vaginal administration, there is a gradual rise to a maximum level at 60 – 120 minutes, but at 240 minutes the level is still at 60% of peak level.

Comparative effectiveness of vaginal and oral administration of misoprostol

(EL Refaey et al. 1995)

- More side effects with oral use
- At similar doses more effective by vaginal route
  - 95% (vaginal) success rate Vs 87% (oral) in first trimester
  - Failure 1% (vaginal) Vs 7% (oral)
- abortion within 4 hours : 93% (vaginal) Vs 78% (oral).

It is assumed that rectal administration results in a similar profile, vaginal dosing therefore can take place with longer intervals

than oral dosing for similar desired uterine effect, and accumulation above 'safe' levels with undesirable side effects can take place. With oral and vaginal dosing of upto 400μg every 3 hours, no accumulation has been noted. Potential hypertonus as a result of drug accumulation could lead to :

- Uterine rupture in the second or third trimester
- Fetal distress in the third trimester
- High rates of nausea and diarrhoea in all trimesters.

For obstetrical use, the vaginal application has been studied the most. Misoprostol in the first and second trimesters is an effective pregnancy termination agent either as a single agent or as an adjunct.

In our study misoprostol has been used vaginally in dose of 400μg 4 hourly as mid-trimester abortifacient along with oxytocin as and when needed. Misoprostol in this dose has been compared to traditional use of dinoprostone in 0.5 mg 12 hourly dosage.

Different studies have been done using misoprostol either alone or with adjuncts using different protocols for mid-trimester abortion. The abortifacient dose of misoprostol is in between 50-800μg and the exact dose schedule is yet to be decided.

Bugalho et al. In 1993 used 200μg to 800μg misoprostol intra-vaginally every 24 hourly with success rate of 91% within 48 hours and mean induction abortion interval of 14.3 hours.

Jain and Mishell in 1994 compared 200μg 12 hourly intravaginal misoprostol with 20μg vaginal gemeprost 3 hourly and found 89% success rate with misoprostol compared to 81% success

rate with gemeprost and mean induction abortion intervals were 12 hrs and 10.6 hrs respectively.

Jain and Mishell in 1996 compared 200μg 12 hourly intravaginal misoprostol with combination of misoprostol + laminaria tent and found 84.80% success rate with misoprostol alone compared to 91% success rate when used with laminaria tent. Mean induction abortion intervals were 15.7 hrs and 17.4 hrs respectively.

Batioglu et al. in 1997 gave 200μg oral misoprostol 1 hourly (maximum 6 doses) and repeated on 2nd day if no abortion occurred. The success rate was 92.9% within 48 hrs and mean induction abortion interval was 9 hrs.

Srisomboon in 1997 used 200μg cervicovaginal misoprostol 12 hourly and success rate was 54% within 12 hours and 92% within 48 hours with mean induction abortion interval of 27.5 hours.

Carbonell et al in 1998 used 800μg vaginal misoprostol 24 hourly for 3 doses with success rate of 80% and mean induction abortion interval of 9.1 hours.

Dickinson et al in 1998 compared 200μg 6 hourly vaginal misoprostol (maximum 4 doses) with 1 mg vaginal geneprost 3 hourly (maximum 5 doses) with success rate of 74.9% within 24 hours for misoprostol and 75.1% for gemeprost. Mean induction abortion intervals were 16.9% hours and 13.7% hours respectively.

Herabutya et al in 1998 used 200μg and 600μg vaginal misoprostol 12 hourly for 48 hours and found success rate of 70.60%,

82.0% and 96.0% respectively. Mean induction abortion interval were 45 hours, 33.4 hours and 22.3 hours respectively.

Wong KS et al in 1998 compared 400μg 3 hourly vaginal misoprostol with 1 mg 3 hourly vaginal gemeprost and found success rates of 80% and 58.6% within 24 hours respectively. Mean induction abortion interval was 14.1 hours and 19.5 hours respectively.

Ghorab et al in 1998 compared extra-amniotic PGF2 with intra-cervical misoprostol and found abortion was complete in 65% and 85% cases respectively.

Premila W. Ashok et al in 1999 used miferpristone 200 mg orally in women for mid-trimester abortion, followed 36-48 hours by intra-vaginal misoprostol 800μg. Further, oral misoprostol 400μg was administered at 3 hourly interval (maximum 4 dose) 97% women aborted successfully either within 5 doses of misoprostol or within 15 hours of first dose of misoprostol.

Jain et al in 1999 compared 200μg vaginal misoprostol 6 with 200μg vaginal misoprostol 12 hourly and found success rate of 87.2% and 89.2% in 48 hours respectively. Mean induction abortion intervals was 13.8 hours and 14 hours respectively.

Herabutya et al in 2000 used 600μg vaginal misoprostol 12 hourly until abortion and found 93% success rate within 72 hours and mean induction abortion interval was 24.1 hours.

Wong KS et al in 2000 compared 400μg vaginal misoprostol 3 hourly with 400μg 6 hourly and found success rates of 90.5% and

75.7% within 48 hours. Mean induction abortion interval was 15.2 hours 19 hours respectively.

Herabutya et al in 2001 compared 600μg vaginal misoprostol 12 hourly with 800μg vaginal misoprostol 12 hourly and found success rate of 92.5% and 92.15% within 48 hours. Mean induction abortion interval was 15.2 hours and 15.3 hours respectively.

Pongasta et al in 2001 used 400μg vaginal misoprostol gel (formed by crushing the tablet and mixing with K-Y jelly) 12 hourly and found mean induction abortion intervals of 35.58 hours.

Hidar S et al in 2001 compared 200μg misoprostol vaginal 12 hourly with 200μg misoprostol vaginal combined with oxytocin infusion. The abortion was successfully in 90% and 95% at 48 hours.

Gonjalez et al in 2001 compared 200μg vaginal misoprostol 6 hourly in admitted patients with same dosage self administrated by patients at home and found mean induction abortion interval of 12 hours and 14 hours respectively.

Dickinson et al in 2002 compared 200μg 6 hourly with 400μg 6 hourly and also with 200μg vaginal misoprostol (following a loading dose of 600μg) and the success rates were 59%, 76% and 80% respectively within 24 hours with mean induction absorption interval of 18.2 hours, 15.1 hours and 13.2 hours respectively.

MATERIAL & METHODS

MATERIAL AND METHODS

The present study was conducted in the department of obstetrics and gynaecology, Maharani Laxmi Bai Medical College, Jhansi. The aim was to compare the efficacy, safety and tolerance of intra-vaginal misoprostol with the use of intra-cervical misoprostol in mid-trimester abortion. A total of 240 patients were recruited for this study. Total number of patients were divided into two study groups (of 120 each) A & B.

Patients for this study were selected from the women attending the gynae O.P.D of department of obstetrics & gynaecology and who had come for medical termination of pregnancy. They were fully counselled and were admitted in the hospital for termination.

A detailed history was taken which included the age, address, parity, socioeconomic status, period of gestation and status. Detailed history regarding the present pregnancy, including a full past obstetric history was also noted. All particulars regarding the numbers of children, their age, sex, number of previous abortion and also history of previous uterine surgery was noted. Lastly, a full family history of any chronic ailments in the patients were also enquired. Finally full consent was taken.

A complete examination of patient was done which includes –

General examination

- General condition
- Pulse
- Blood pressure
- Body temperature

- Respiratory rate
- Pallor
- Icterus
- Cyanosis
- Oedema
- Clubbing
- Lymphadenopathy

Systemic examination

- Respiratory system
- Cardio-vascular system
- Central nervous system

Per-abdominal examination

- To see the fundal height and look for any organomegaly, if present.

Pelvic examination

- Per speculum examination for any local pathology in vagina and cervix.
- Per vaginal examination for assessment of uterine size, mobility and to rule out pelvic pathology, if any.

Investigations included

- Hb%
- Rh typing, if necessary
- Urine routine and microscopic examination

To each case, prior to application of misoprostol or dinoprostone tetanus toxoid was given with a single dose of injectible antibiotic.

Selection criteria for study were :

1. Age 18 - 45 yrs
2. Parity 0 - 5
3. Uterine size > 12 – 20 weeks

Exclusion criteria for both groups was :

1. Uterine scar either caesarean or myomectomy.

Exclusion criteria for dinoprostone group :

1. Bronchial asthma
2. Cardiac disease

Procedure

In each patient, part was prepared, consent was taken, injection tetanus toxoid and a single shot of injectible antibiotic was given. Patient was asked to empty bladder. Pelvic examination was done under strict aseptic conditions and group A patients were applied misoprostol 400µg, 4 hourly intra-vaginally in posterior fornix in powder form by crushing the tablets. Two tablets were placed in posterior fornix in powder form. Each tablet used in study was of 200µg strength. Group B patients were applied intra-cervical dinoprostone gel (0.5 mg) 12 hourly.

All patients were monitored for cervical ripening and dilatation, uterine contractions and induction abortion interval and side effects such as bleeding per vaginum, nausea, vomiting, and fever etc. oxytocin supplementation was done as and when required in both groups.

Misoprostol was given 400µg, 4 hourly upto 3 doses and if patient did not abort after three doses, they were applied two more

doses after a rest of 8 – 12 hours. Total five doses were used for misoprostol group.

In dinoprostone group, patients were applied dinoprostone gel 0.5 mg, 12 hourly for two doses and if patient did not abort one more dose was applied after a rest of 8-12 hours. Maximum three doses of dinoprostone were used.

Following abortion, a pelvic examination was done to check completeness of abortion. The cervix was explored for any cervical injury. Incomplete abortions were managed with oxytocin drip and surgical evacuation. Patients were discharged 12-24 hours after abortion.

The trial was considered successful, when the patient aborted within 40 hours. Any case was taken as a failure if it did not abort within the above-mentioned period.

OBSERVATIONS

OBSERVATION

This study consists of 240 cases who appeared in the Out Patients Department of M.L.B. Medical College Jhansi for termination of pregnancy from 12-20 weeks of gestation. In this study patients were randomized in two study groups A & B. In group A patients were applied misoprostol 400 µg 4 hourly and group B patients were applied dinoprostone gel 0.5 mg 12 hourly. Maximum 5 doses of misoprostol and 3 doses of dinoprostone were used for study. The observations during the study can be summarized in following tables.

TABLE – I

AGE DISTRIBUTION OF PATIENTS IN MISOPROSTOL GROUP

S. No	Age in years	No. of cases	Percentage
1	18 – 25	30	25.0
2	25 – 30	48	40.0
3	30 – 35	32	26.66
4	35 – 40	08	6.66
5	40 - 45	02	1.66
	Total	**120**	**100%**

The above table shows that the maximum numbers of patients are in the age group of 25-30 years and least common is the age of 40-45 years. Mean age is 28.25 years.

AGE DISTRIBUTION OF PATIENTS IN MISOPROSTOL GROUP

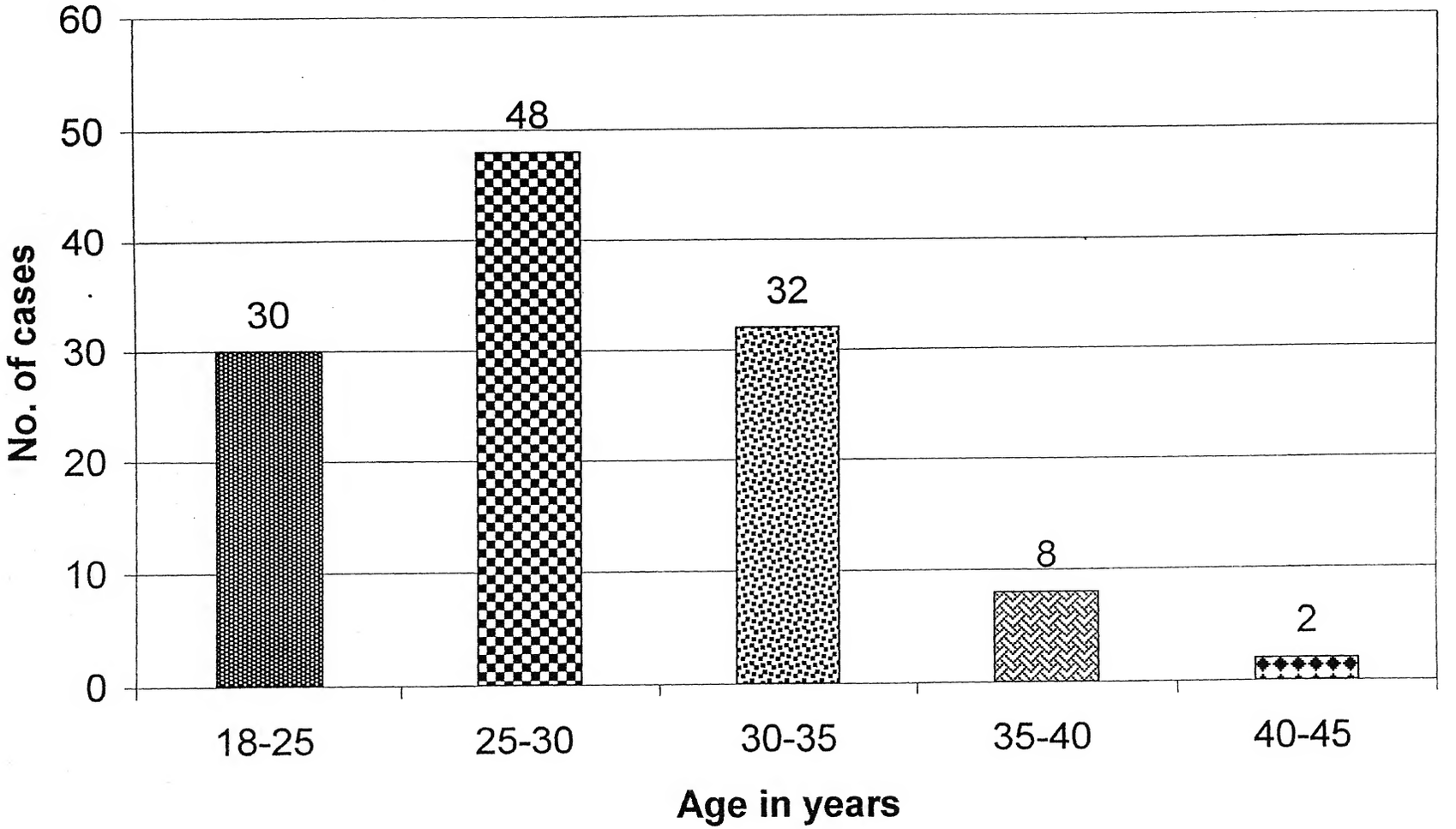


TABLE – II

AGE DISTRIBUTION OF PATIENTS IN DINOPROSTONE GROUP

S. No	Age in years	No. of cases	Percentage
1	18 – 25	28	23.33
2	25 – 30	52	43.33
3	30 – 35	30	25.0
4	35 – 40	06	3.0
5	40 - 45	04	3.33
	Total	**120**	**100%**

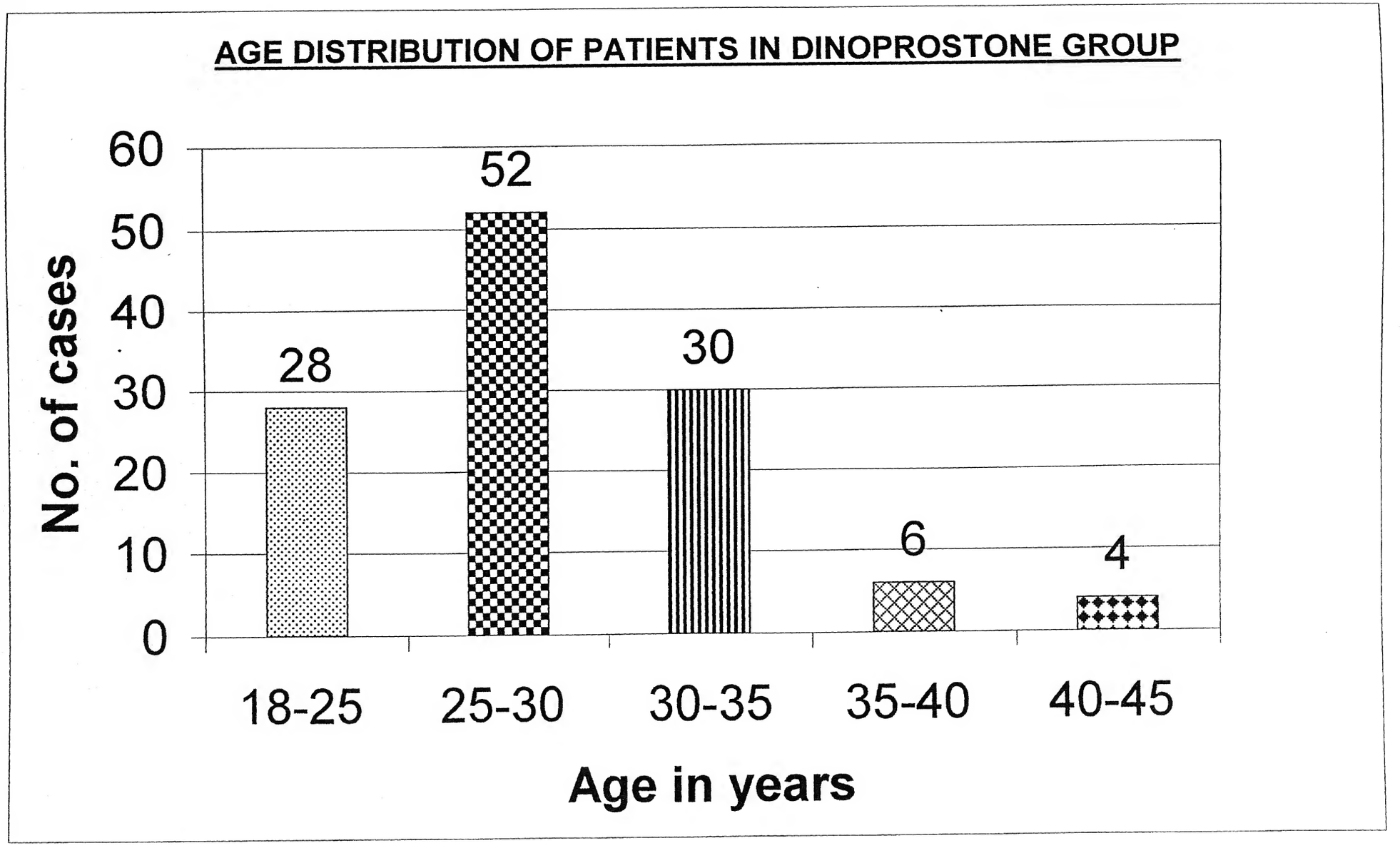
The above table shows that the most common age group was of age of 25-30 years and least common was of 40-45 years. Mean age is 28.35 years.

TABLE – III

SHOWING CASES IN RELATION TO PARITY IN MISOPROSTOL GROUP

S. No	Parity	No. of cases	Percentage
1	Po	08	6.66
2	P1	03	2.50
3	P2	34	28.33
4	P3	39	32.50
5	P4	30	25.0
6	P5	06	5.0
	Total	**120**	**100%**

The above table shows the incidence of patients in relation to parity. Maximum no. of patients were multiparas because in India termination is used for spacing the birth of babies as well as to limit the family size.


AGE DISTRIBUTION OF PATIENTS IN DINOPROSTONE GROUP
No. of cases
60
50
40
30
20
10
0
28
52
30
6
4
18-25
25-30
30-35
35-40
40-45
Age in years

SHOWING CASES IN RELATION TO PARITY IN MISOPROSTOL GROUP

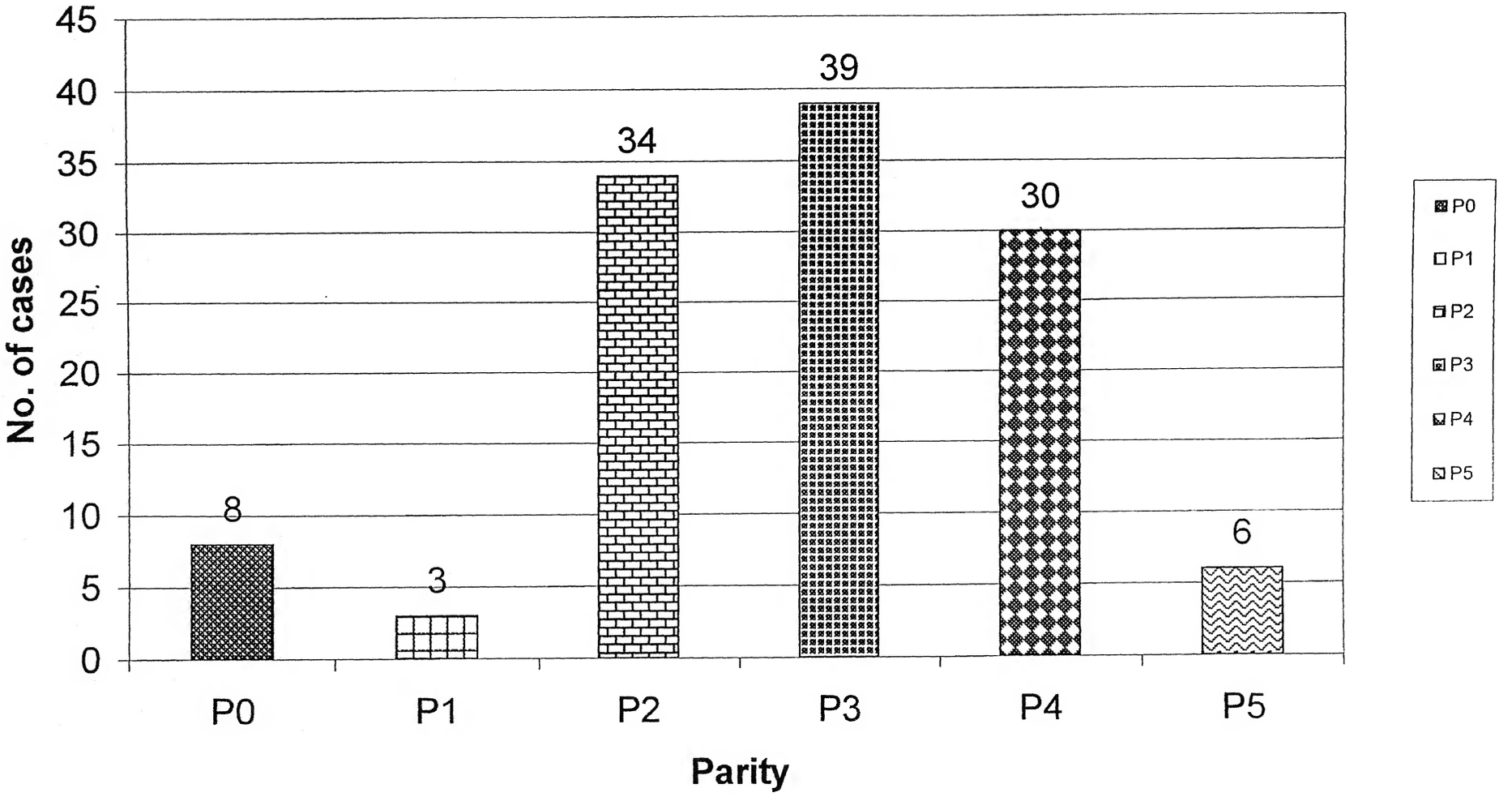


TABLE – IV
SHOWING CASES IN RELATION TO PARITY IN DINOPROSTONE GROUP

S. No	Parity	No. of cases	Percentage
1	Po	12	10.0
2	P1	02	5.0
3	P2	30	25.0
4	P3	40	33.33
5	P4	28	23.33
6	P5	08	6.66
	Total	**120**	**100%**

The above table shows that in majority patients were multipara with maximum incidence of P3.

TABLE - V
SHOWING RELATION OF MARITAL STATUS IN MISOPROSTOL GROUP

S. No	Marital status	No. of cases	Percentage
1	Unmarried	12	10.0
2	Married	92	76.66
3	Widow	08	6.66
4	Divorcee	08	6.66
	Total	**120**	**100%**

The above table shows that majority of cases who came for mid-trimester abortion were married. Least common group was of widows.

TABLE – IV
SHOWING CASES IN RELATION TO PARITY IN DINOPROSTONE GROUP

S. No	Parity	No. of cases	Percentage
1	Po	12	10.0
2	P1	02	5.0
3	P2	30	25.0
4	P3	40	33.33
5	P4	28	23.33
6	P5	08	6.66
	Total	**120**	**100%**

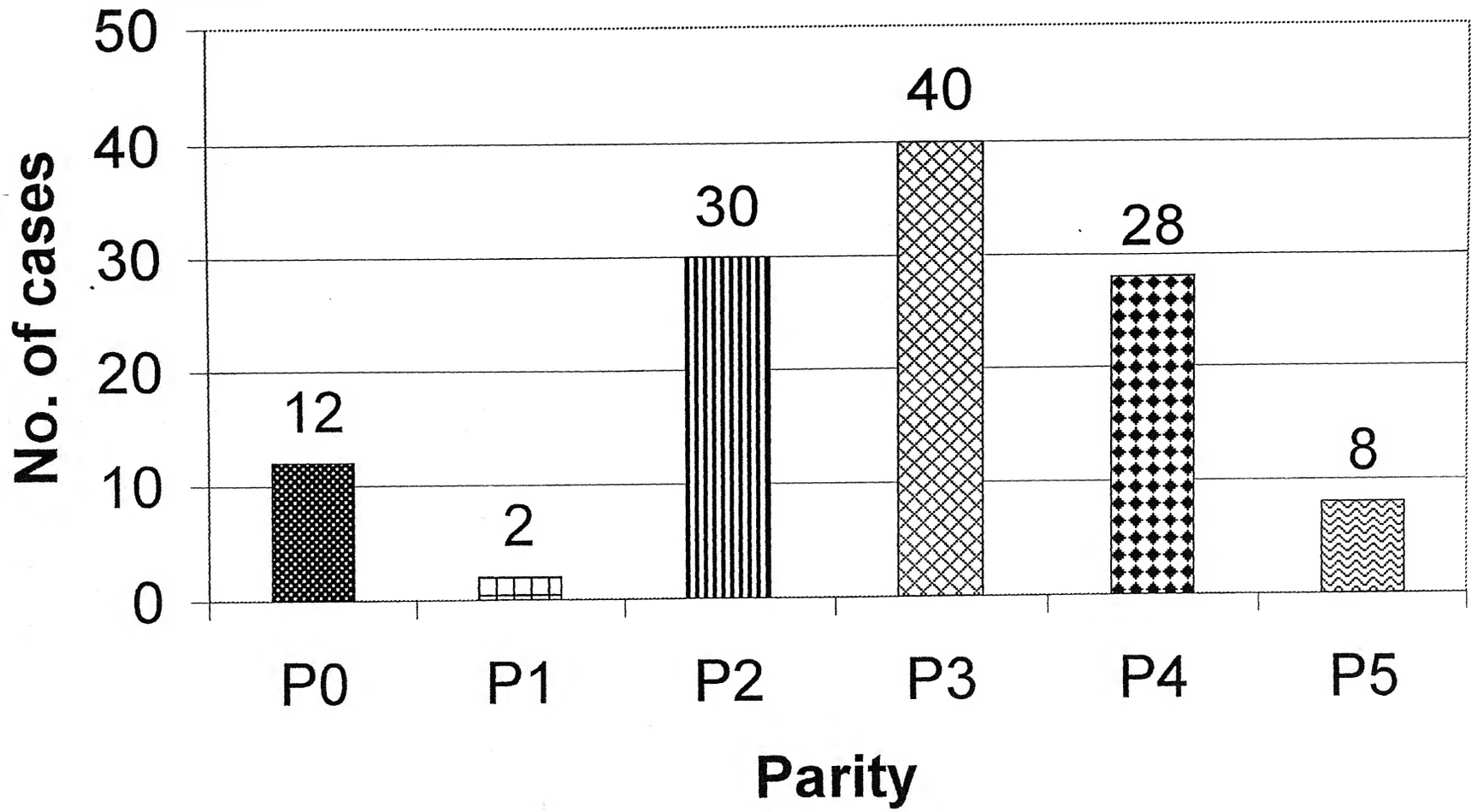
The above table shows that in majority patients were multipara with maximum incidence of P3.

TABLE - V
SHOWING RELATION OF MARITAL STATUS IN MISOPROSTOL GROUP

S. No	Marital status	No. of cases	Percentage
1	Unmarried	12	10.0
2	Married	92	76.66
3	Widow	08	6.66
4	Divorcee	08	6.66
	Total	**120**	**100%**

The above table shows that majority of cases who came for mid-trimester abortion were married. Least common group was of widows.

SHOWING CASES IN RELATION TO PARITY IN DINOPROSTONE GROUP



SHOWING RELATION OF MARITAL STATUS IN MISOPROSTOL GROUP

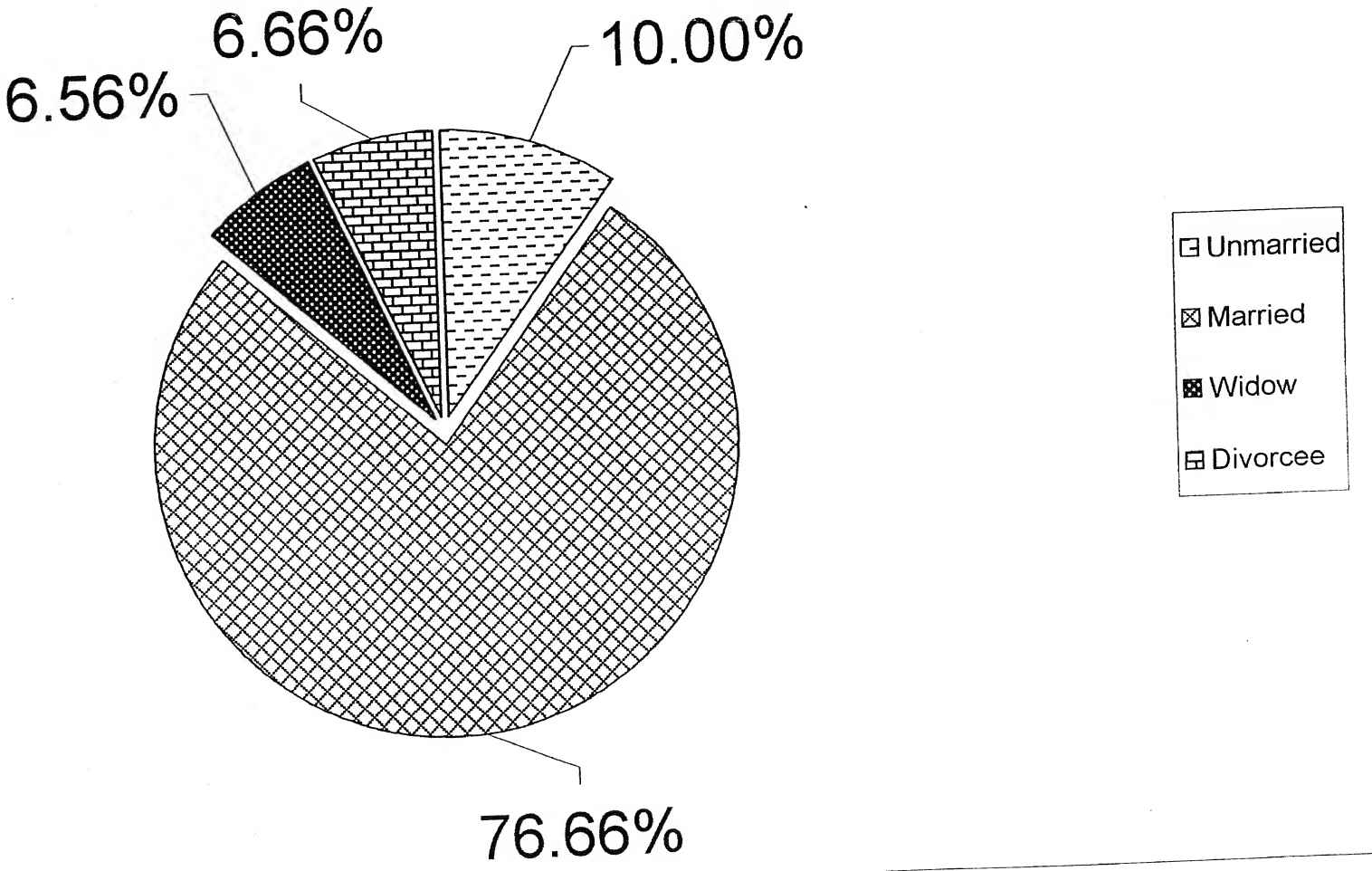


TABLE - VI

SHOWING RELATION OF MARITAL STATUS IN DINOPROSTONE GROUP

S. No	Marital status	No. of cases	Percentage
1	Unmarried	19	15.83
2	Married	86	72.66
3	Widow	06	5.0
4	Divorcee	09	7.50
	Total	**120**	**100%**

The above table shows that majority of cases were married and least common group was of widows.

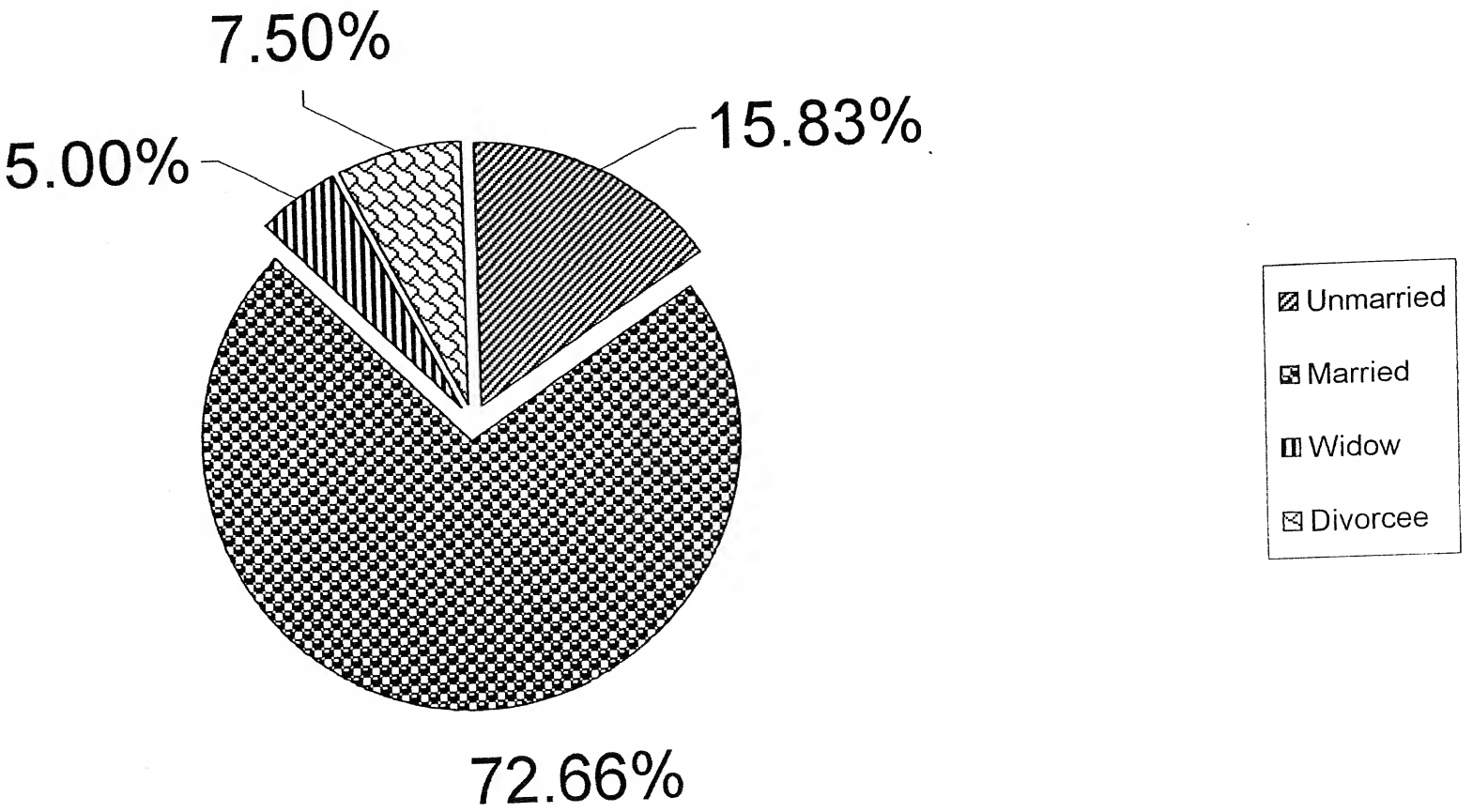
TABLE - VII

SHOWING DISTRIBUTION OF URBAN/RURAL POPULATION IN MISOPROSTOL GROUP

S. No	Marital status	No. of cases	Percentage
1	Urban	38	31.66
2	Rural	82	68.33
	Total	**120**	**100%**

The above table shows that majority of patients came from rural areas.

SHOWING RELATION OF MARITAL STATUS IN DINOPROSTONE GROUP



SHOWING DISTRIBUTION OF URBAN / RURAL POPULATION IN MISOPROSTOL GROUP

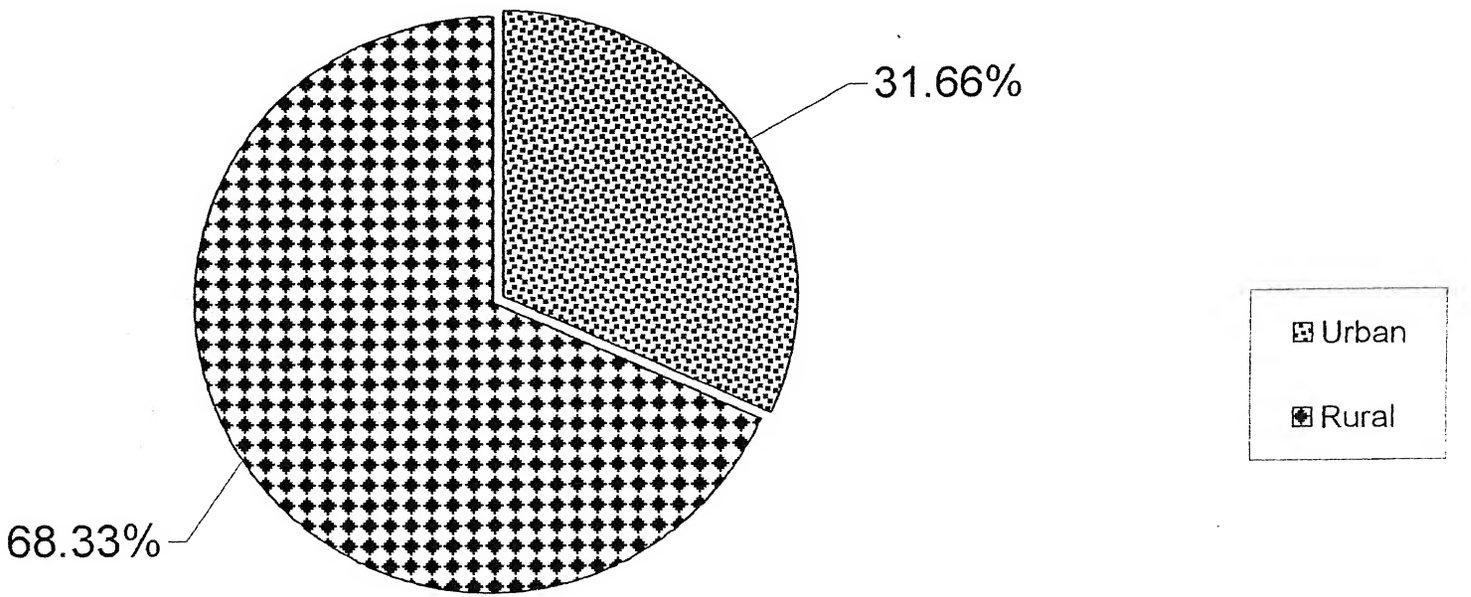


TABLE - VIII

SHOWING DISTRIBUTION OF URBAN/RURAL POPULATIONIN DINOPROSTONE GROUP

S. No	Marital status	No. of cases	Percentage
1	Urban	40	33.33
2	Rural	80	66.66
	Total	**120**	**100%**

The above table shows that majority of patients came from rural areas.

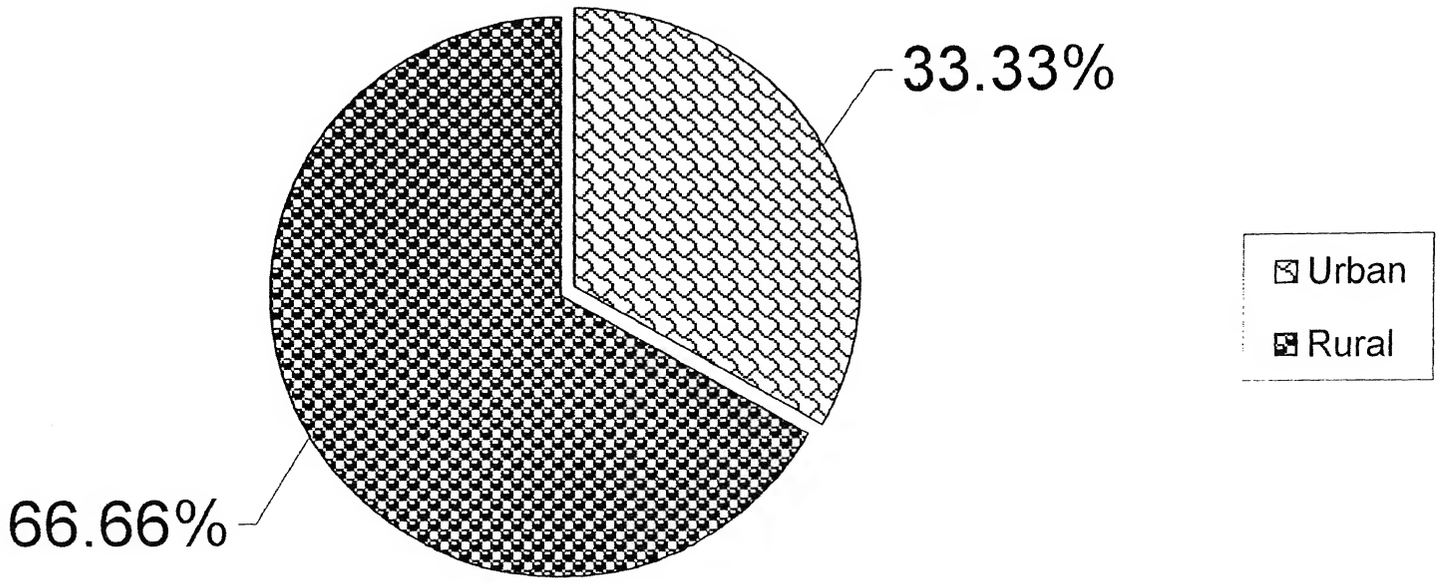
TABLE - IX

SHOWING SOCIO-ECONOMIC STATUS OF PATIENTS IN MISOPROSTOL GROUP

S. No	Socio-economic status	No. of cases	Percentage
1	Low	68	56.66
2	Middle	30	25.0
3	Higher	22	18.33
	Total	**120**	**100%**

The above table shows that maximum cases belonged to low socio-economic status.

SHOWING DISTRIBUTION OF URBAN / RURAL POPULATION IN DINOPROSTONE GROUP



SHOWING SOCIO-ECONOMIC STATUS OF PATIENTS IN MISOPROSTOL GROUP

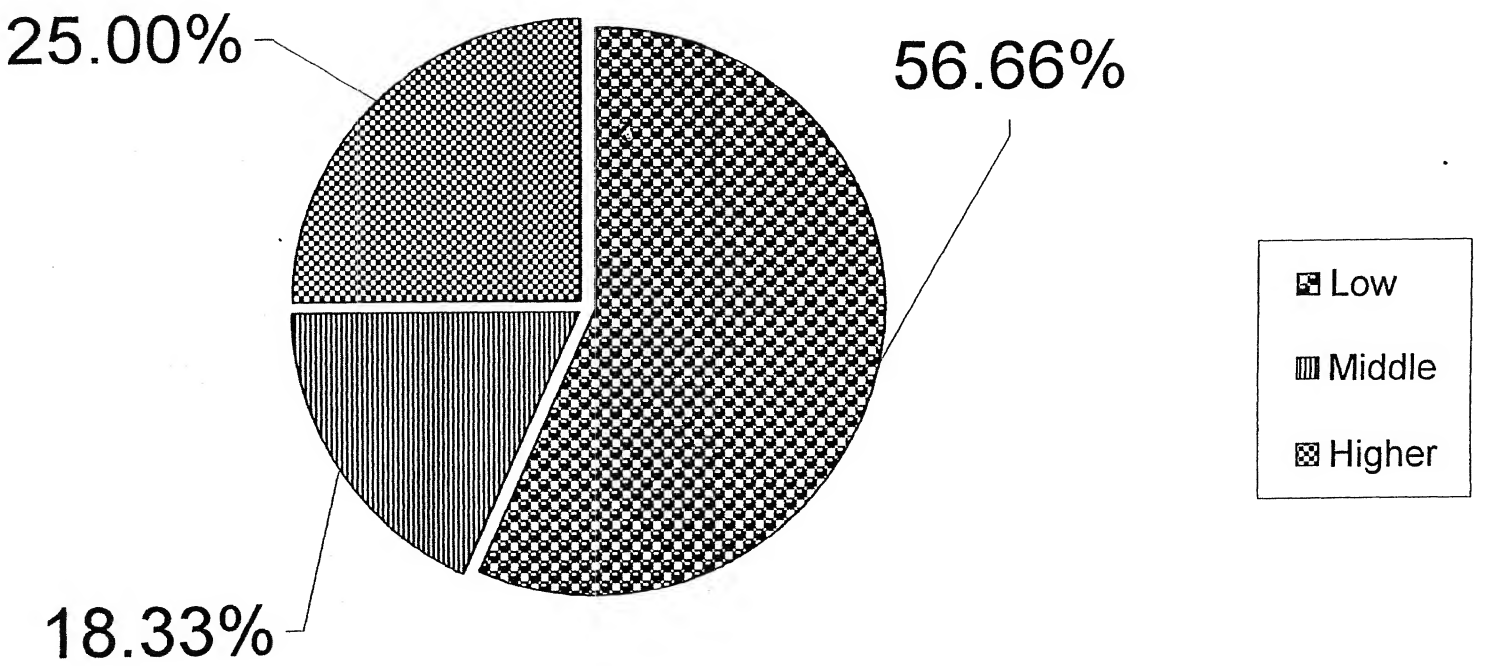


TABLE - X

SHOWING SOCIO-ECONOMIC STATUS OF PATIENTS IN DINOPROSTONE GROUP

S. No	Socio-economic status	No. of cases	Percentage
1	Low	72	60.0
2	Middle	28	23.33
3	Higher	20	16.66
	Total	**120**	**100%**

The above table shows that maximum cases belonged to low socio-economic status.

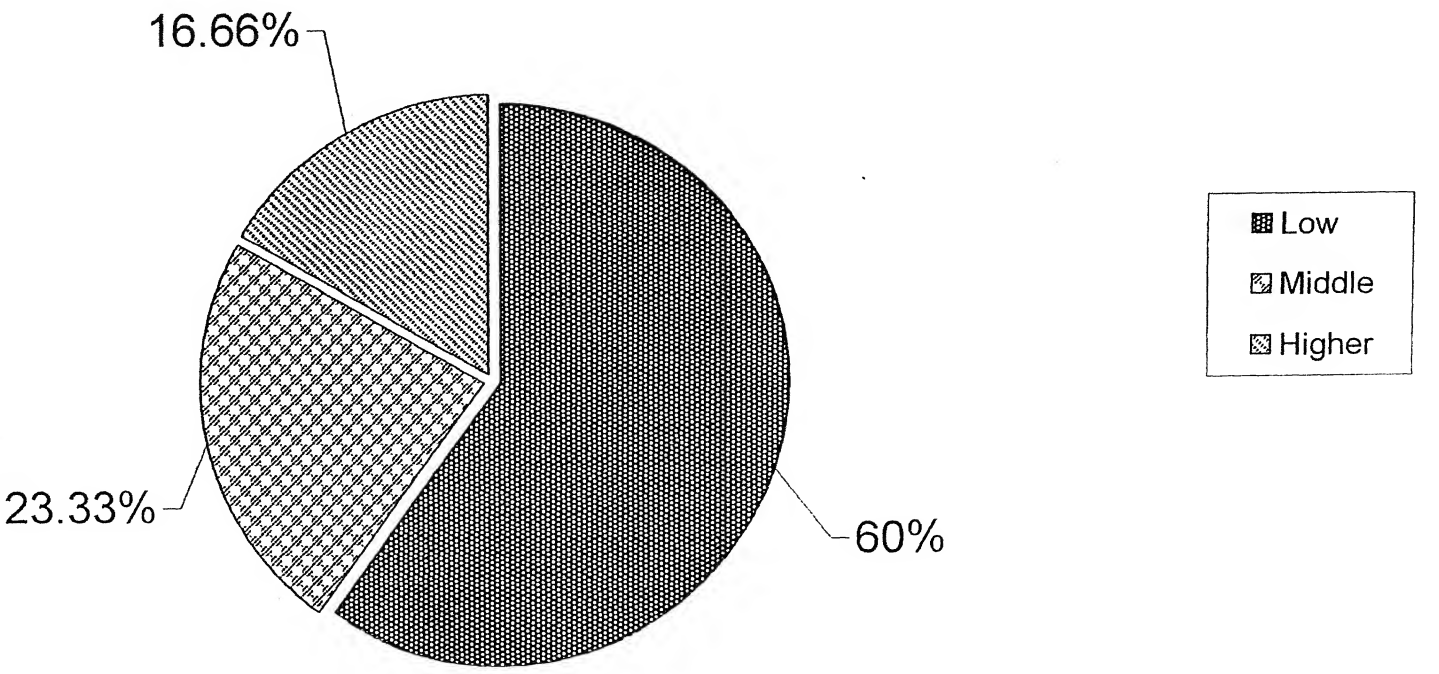
TABLE – XI

SHOWING DISTRIBUTION OF CASES ACCORDING TO GESTATIONAL AGE IN MISOPROSTOL GROUP

S. No	Gestational age in weeks	No. of cases	Percentage
1	12 – 14	22	18.33
2	14 – 16	29	24.16
3	16 – 18	39	32.50
4	18 – 20	30	25.0
	Total	**120**	**100%**

The above table shows distribution of patients according to gestational age. As most of the patients were multipara and of rural origin they presented late so majority were in 16-20 weeks gestational age group. Mean gestational age was 16.28 weeks.

SHOWING SOCIO-ECONOMIC STATUS OF PATIENTS IN DINOPROSTONE GROUP



SHOWING DISTRIBUTION OF CASES ACCORDING TO GESTATIONAL AGE IN MISOPROSTOL GROUP

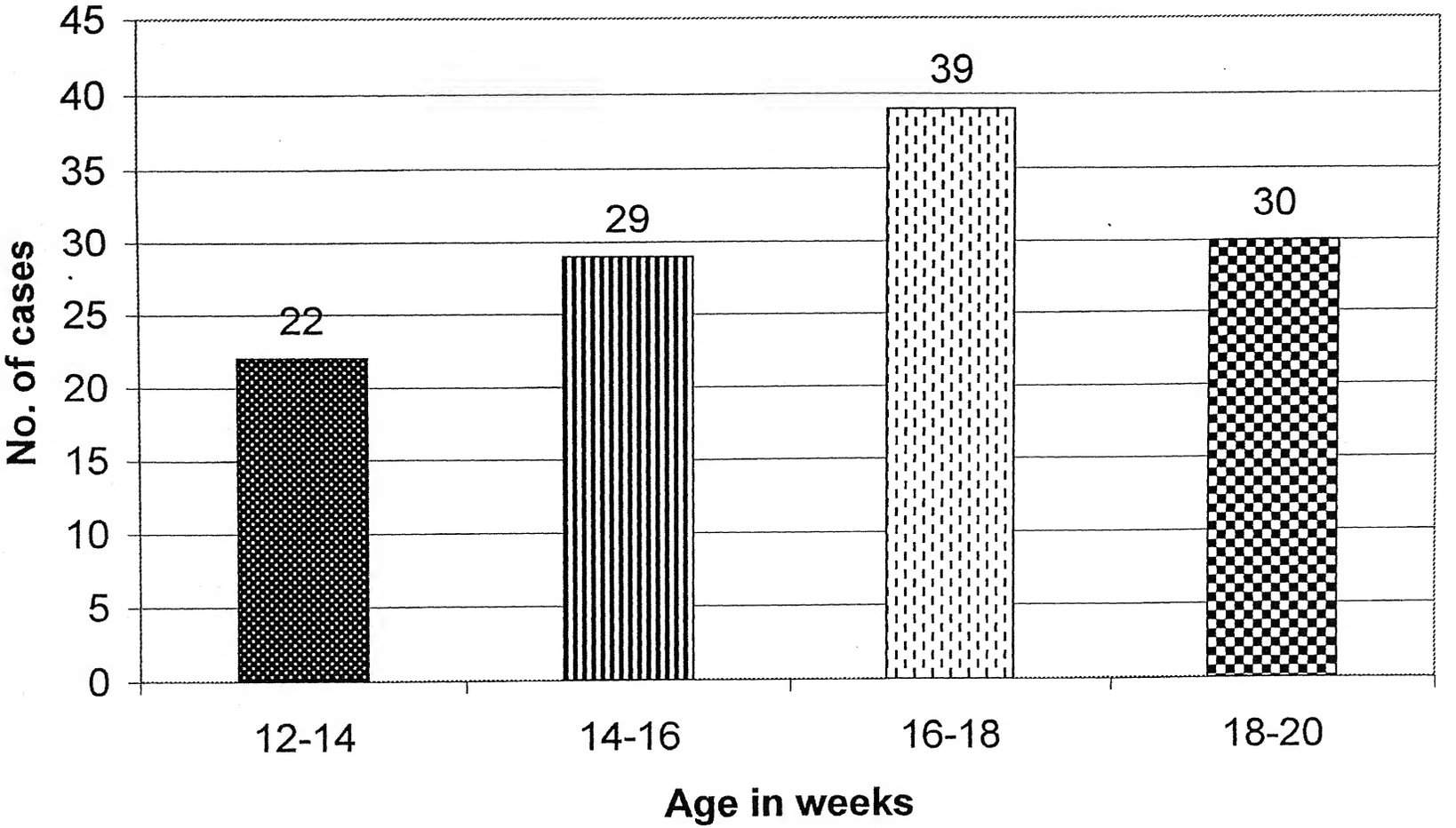


TABLE – XII

SHOWING DISTRIBUTION OF CASES ACCORDING TO GESTATIONAL AGE IN DINOPROSTONE GROUP

S. No	Gestational age in weeks	No. of cases	Percentage
1	12 – 14	21	17.50
2	14 – 16	27	22.50
3	16 – 18	40	33.33
4	18 – 20	32	26.66
	Total	**120**	**100%**

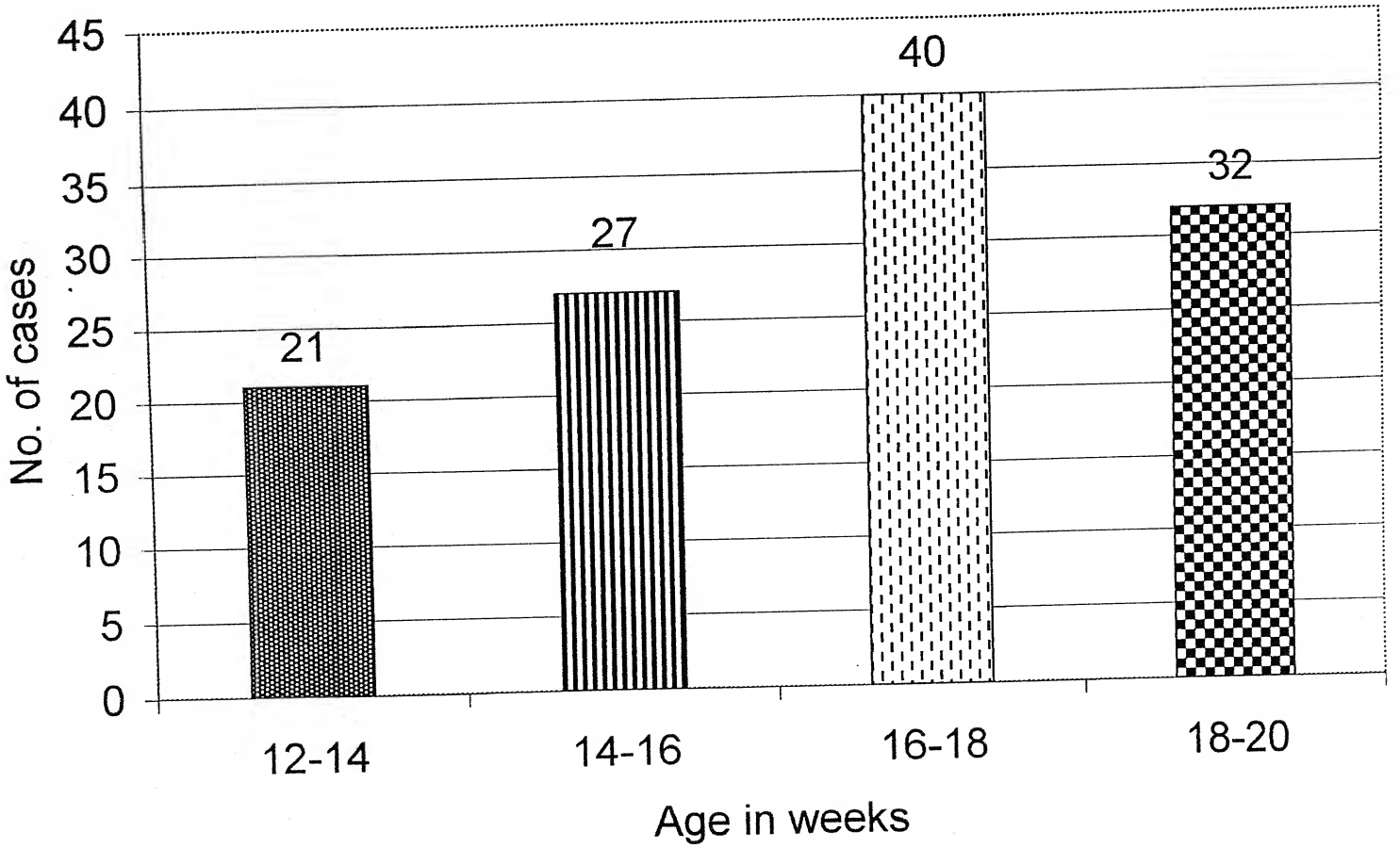
The above table shows that maximum number of patients presented in 16-20 weeks gestational age group. Mean gestational age was 16.38 weeks.

TABLE – XIII

SHOWING VARIOUS PARAMETERS FOLLOWING INDUCTION OF ABORTION BY MISOPROSTOL

S. No	Parameters	No. of cases	Percentage
1	Abortions within 12 hours	92	76.66
2	Abortions within 24 hours	109	90.83
3	Abortions within 40 hours	117	97.50
4	Failed abortions	03	2.50

SHOWING DISTRIBUTION OF CASES ACCORDING TO GESTATION AGE IN DINOPROSTONE AGE



SHOWING VARIOUS PARAMETERS FOLLOWING INDUCTION OF ABORTION BY MISOPROSTOL

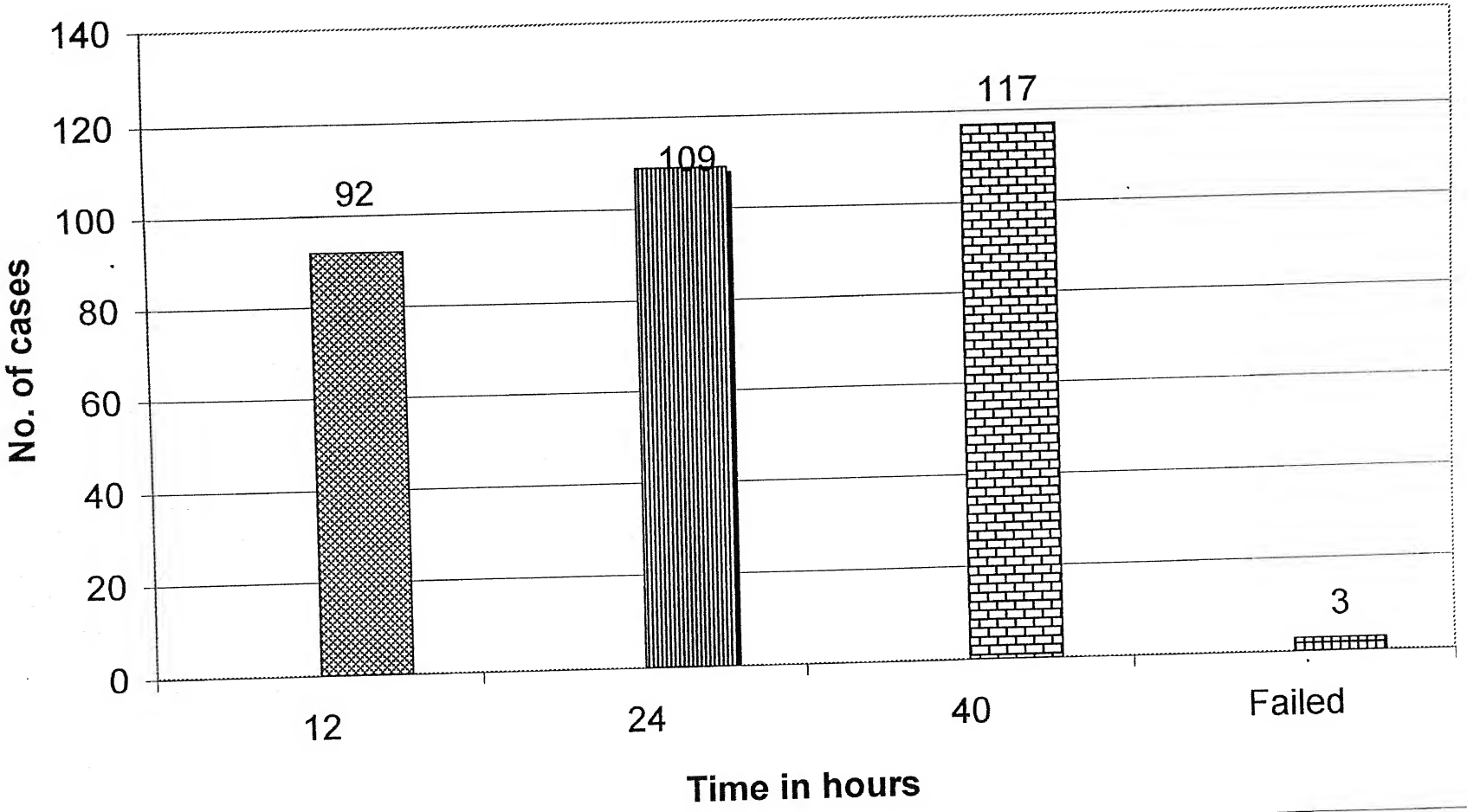


TABLE – XIV

SHOWING VARIOUS PARAMETERS FOLLOWING INDUCTION OF ABORTION BY DINOPROSTONE

S. No	Parameters	No. of cases	Percentage
1	Abortions within 12 hours	50	41.66
2	Abortions within 24 hours	93	77.55
3	Abortions within 40 hours	100	83.33
4	Failed abortions	20	16.77

The above two tables in comparative terms show that misoprostol achieved more abortions within first 24 hours (91% compared to 78% for dinoprostone), and success rate within 40 hours was 97.5% for misoprostol and 83.3% for dinoprostone. Failure rate was 2.5% for misoprostol and 16.7% for dinoprostone.

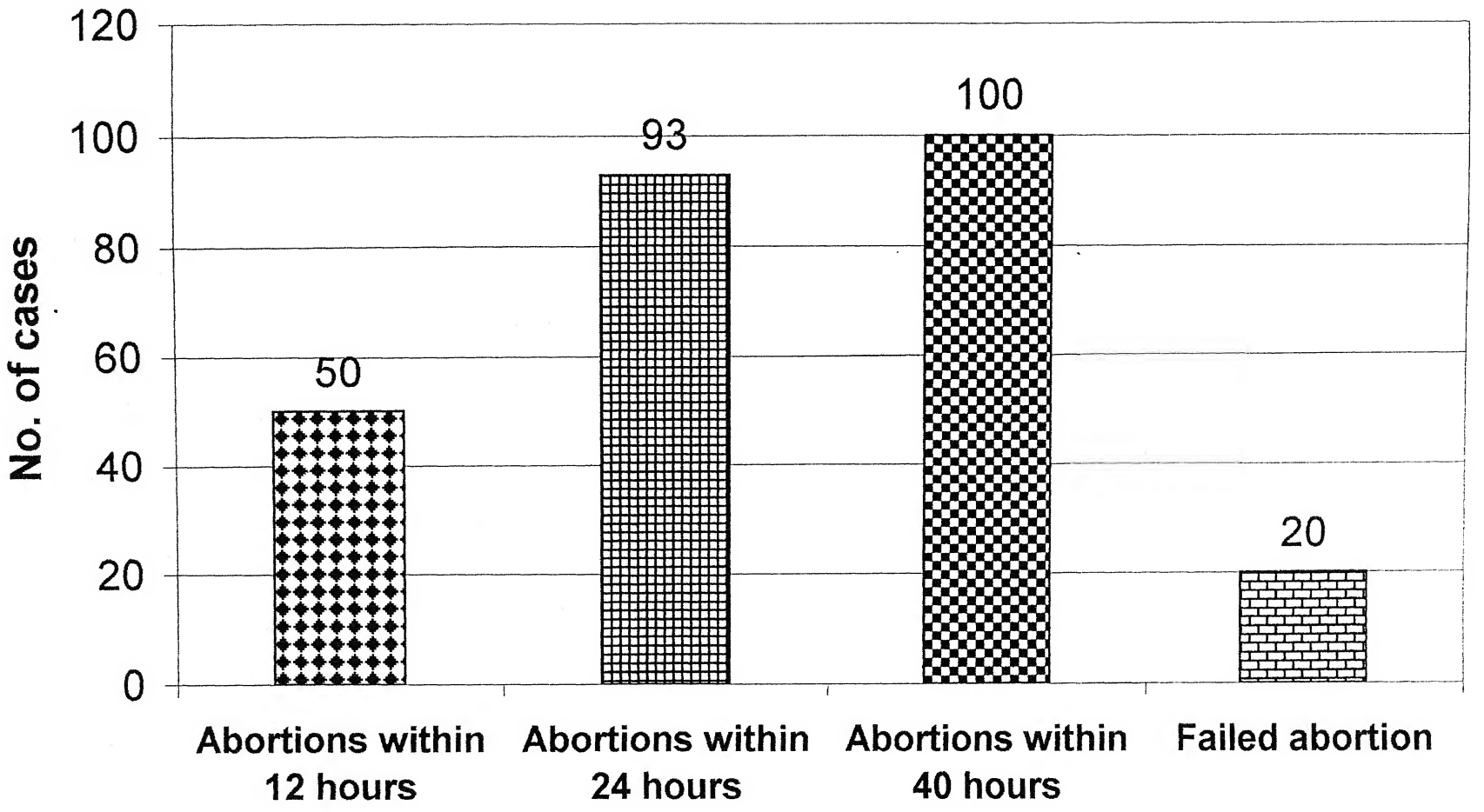
TABLE – XV

SHOWING EFFICACY OF MISOPROSTOL IN RELATION TO DIFFERENT GESTATIONAL AGES

S. No	Gestational age	Induction to abortion interval	Failure of termination
1	> 12 – 16	11.6 hours	3.0
2	> 16 – 20	11.1 hours	2.1

The above table shows that the efficacy of misoprostol did not show any significant variation in relation to duration of gestation.

SHOWING VARIOUS PARAMETERS FOLLOWING INDUCTION OF ABORTION BY DINOPROSTONE



SHOWING EFFICACY OF MISOPROSTOL IN RELATION TO DIFFERENT GESTATIONAL AGES (Failure of termination)

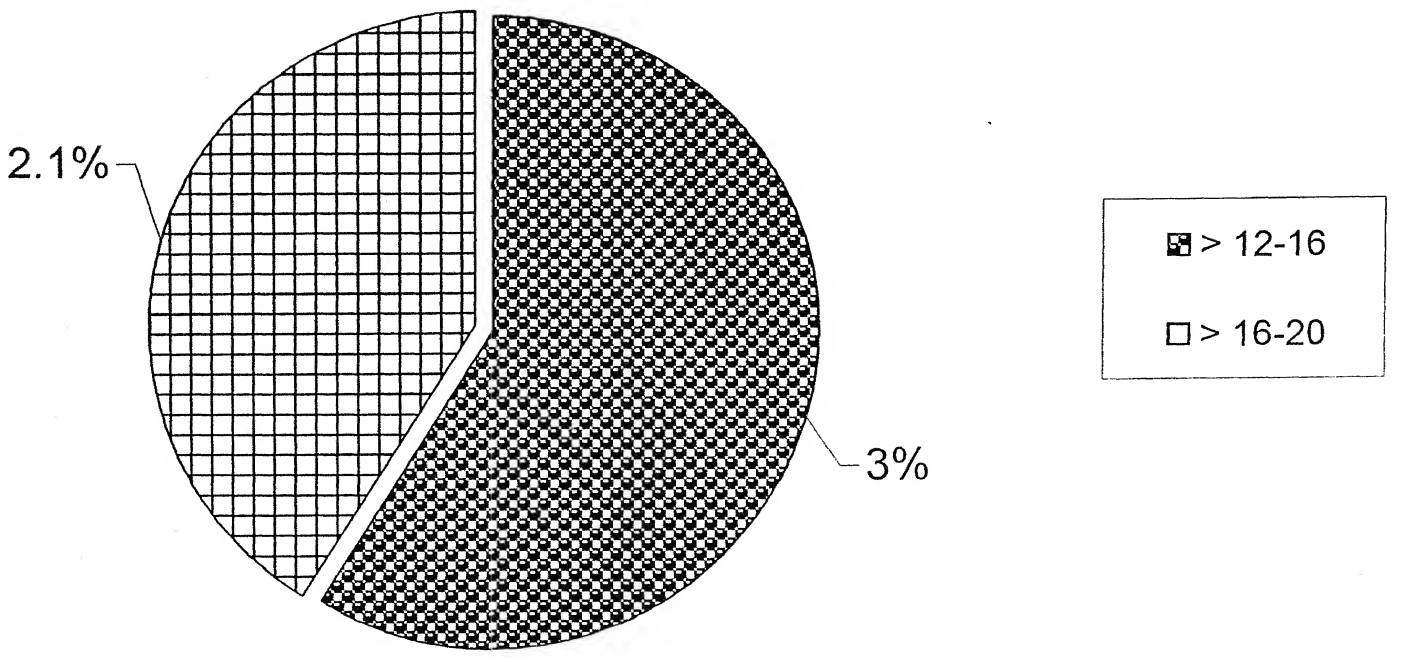


TABLE – XVI

SHOWING MEAN INDUCTION – ABORTION INTERVAL AND MEAN OXYTOCIN USAGE HOURS IN BOTH GROUPS

S. No		Misoprostol	Dinoprostone
1	Mean induction – abortion interval	11.2 ± 6.83 hours	18.1 ± 9.76 hours
2	Oxytocin supplementation	7.2 hours	11.4 hours

The above table shows that misoprostol proved more effective in terms of mean induction – abortion interval ($P<0.01$) and oxytocin requirement was also much less in misoprostol group.

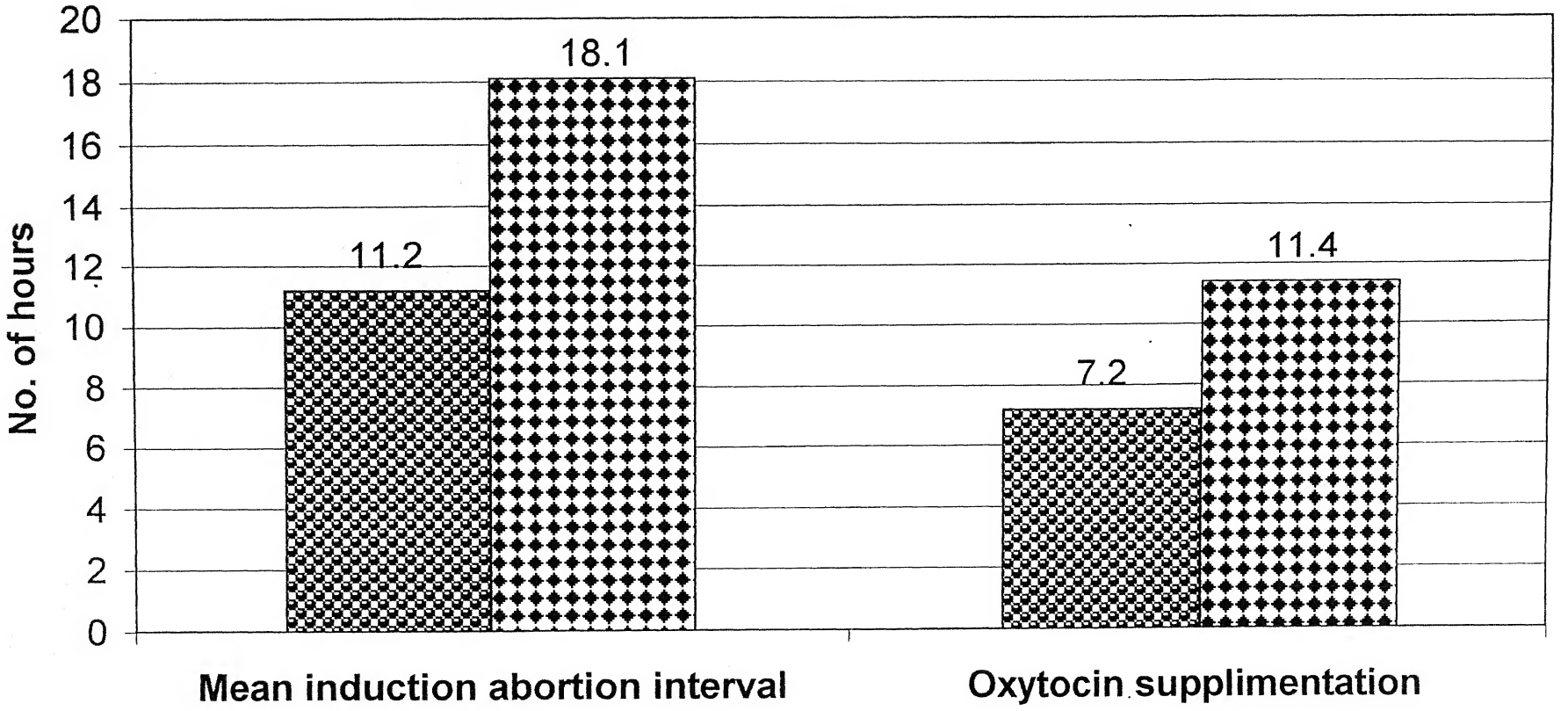
TABLE – XVII

SHOWING SIDE EFFECTS IN MISOPROSTOL GROUP

S. No	Side effects	No. of cases	Percentage
1	Nausea	3	2.5
2	Vomiting	3	2.5
3	Diarrhoea	6	5.0
4	Fever	9	7.5
5	Sever uterine pain	9	7.5
6	Bleeding per vaginum	15	12.5

The above table shows that the incidence of bleeding per vaginum after misoprostol application was the most common side effect followed closely by fever and severe uterine pain.

SHOWING MEAN INDUCTION - ABORTION INTERVAL AND MEAN OXYTOCIN USAGE HOURS IN BOTH GROUPS



SHOWING SIDE EFFECTS IN MISOPROSTAL GROUP

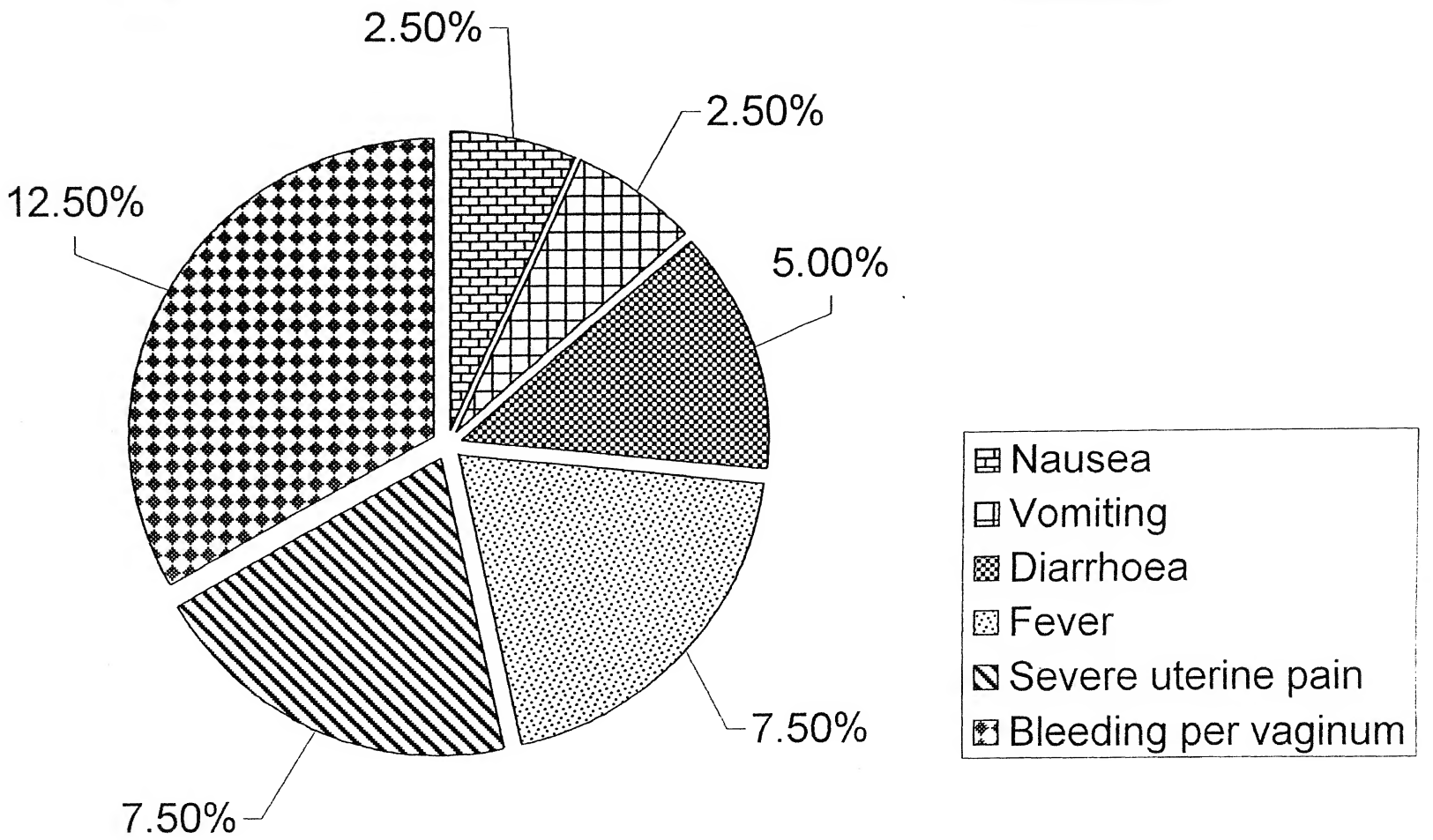


TABLE – XVIII

SHOWING SIDE EFFECTS IN DINOPROSTONE GROUP

S. No	Side effects	No. of cases	Percentage
1	Nausea	9	7.5
2	Vomiting	5	4.22
3	Diarrhoea	9	7.5
4	Fever	2	1.66
5	Sever uterine pain	15	12.5
6	Bleeding pervaginum	3	2.5

The above table shows that the incidence of severe uterine pain was the most common side effect in dinoprostone group followed by nausea, vomiting and dirrhoea.

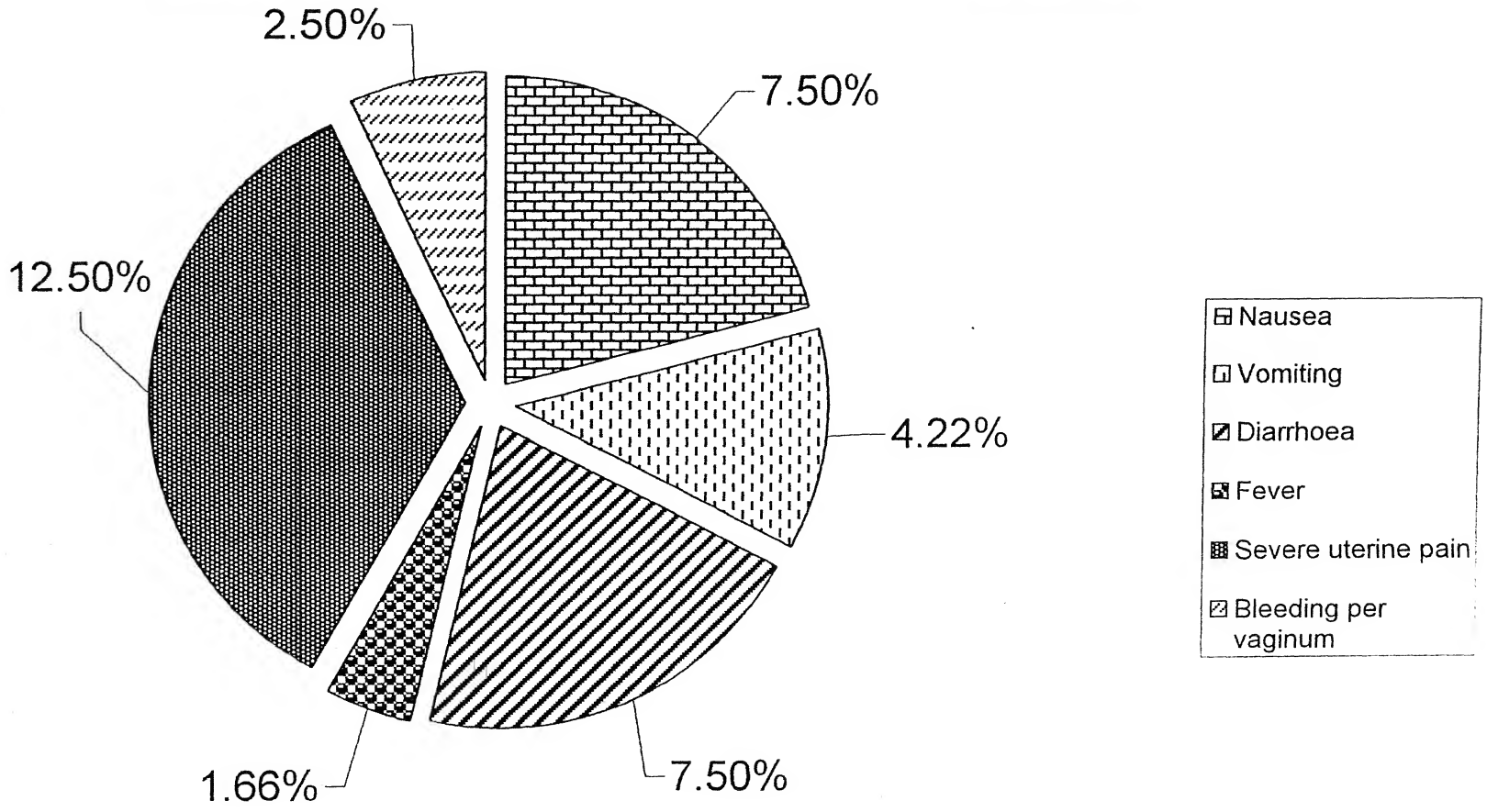
TABLE– XIX

SHOWING DOSAGE OF MISOPROSTOL IN ABORTIONS

S. No	Dose in (μg)	No. of cases	Percentage
1	400	30	25.0
2	800	68	55.66
3	1200	14	11.66
4	2000	08	6.66

The above table shows that the most common dose required was 800μg followed by 400μg.

SHOWING SIDE EFFECTS IN DINOPROSTONE GROUP



SHOWING TOTAL DOSAGE OF MISOPROSTOL IN ABORTIONS

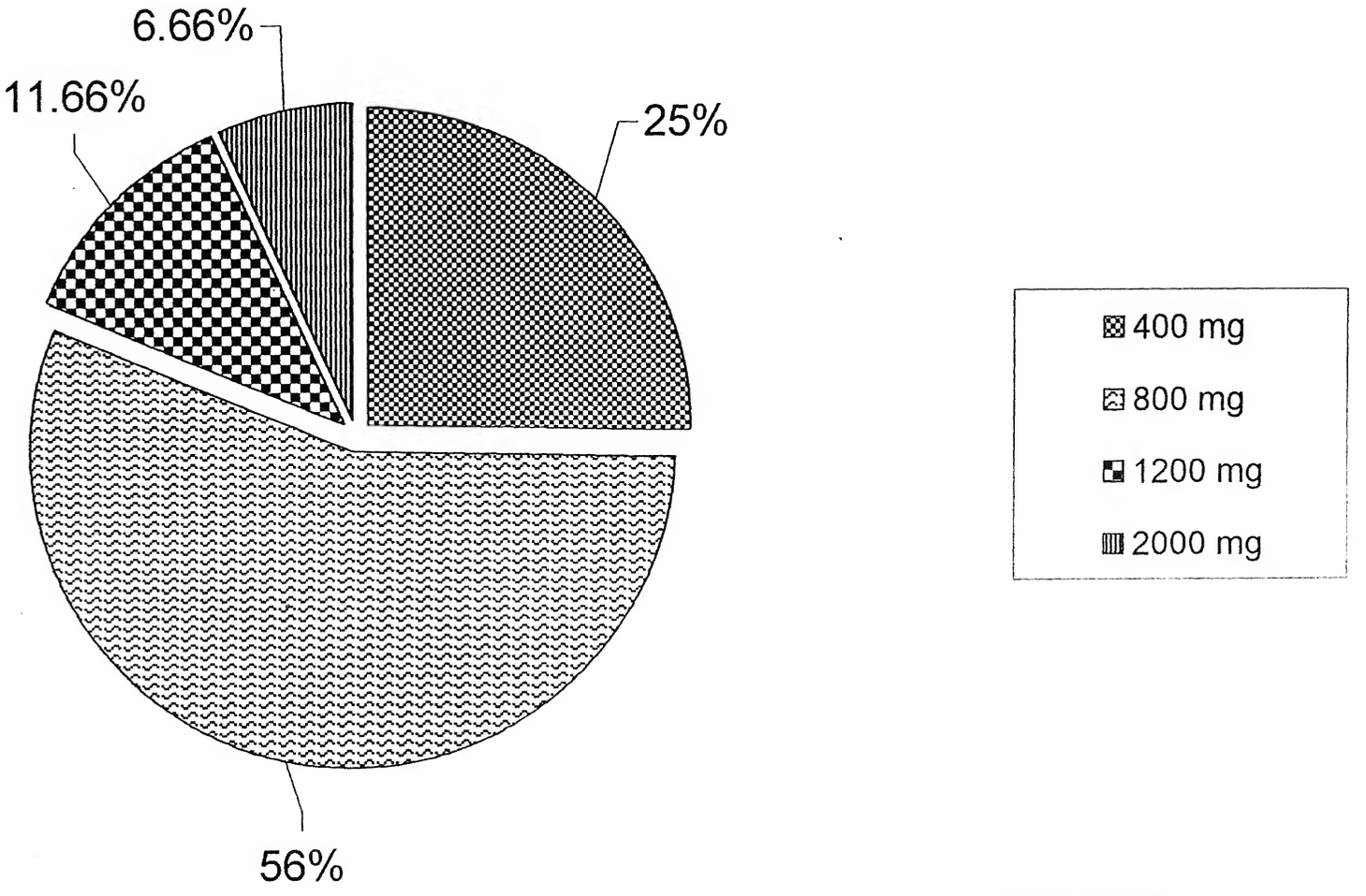


TABLE – XX

SHOWING DOSAGE OF DINOPROSTONE IN ABORTIONS

S. No	Dose in (μg)	No. of cases	Percentage
1	0.5 mg	27	22.55
2	1.0 mg	66	55.0
3	1.5 mg	07	5.88

The above table shows that the most common dose required was 1.0 mg for dinoprostone.

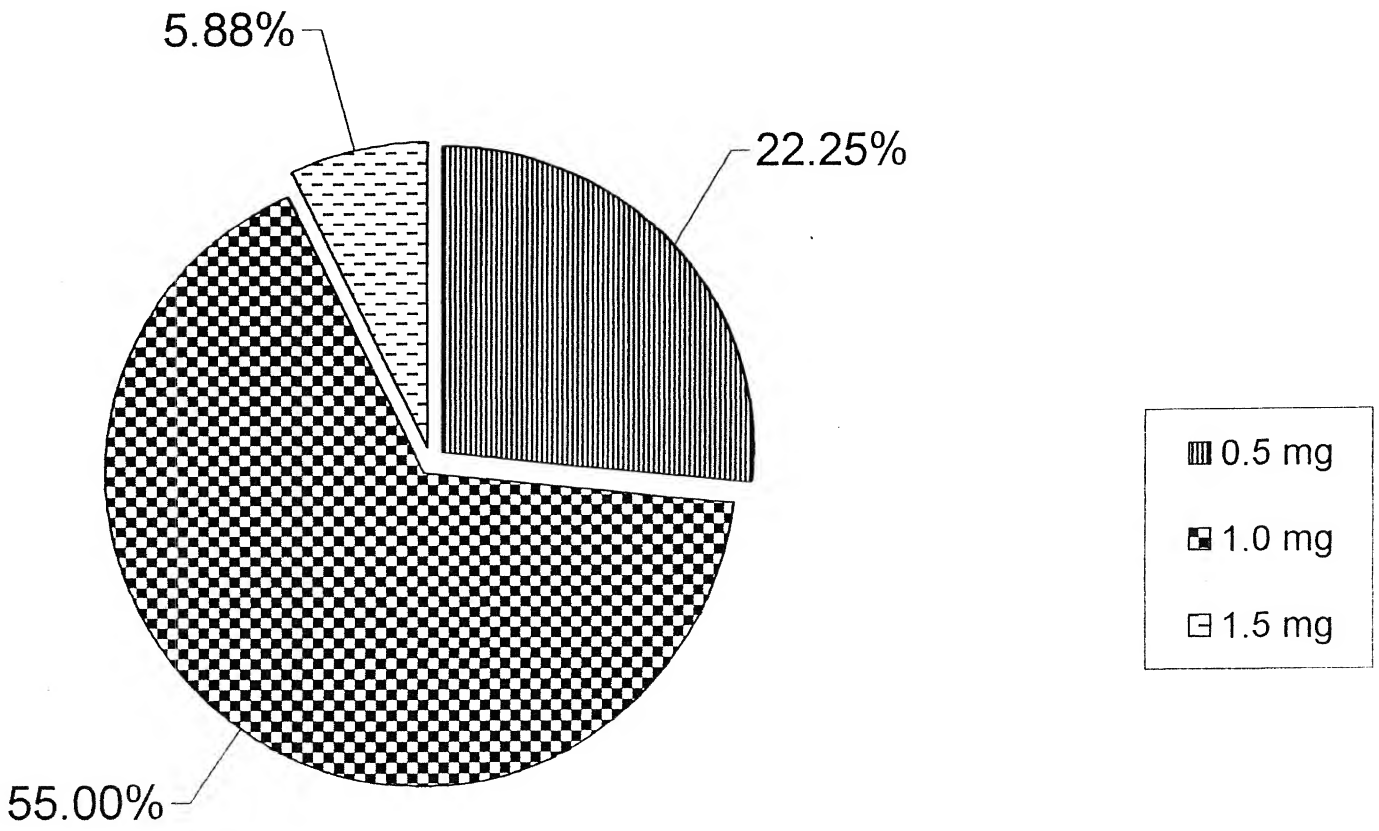
TABLE – XXI

SHOWING MODE OF MANAGEMENT OF FAILED CASES

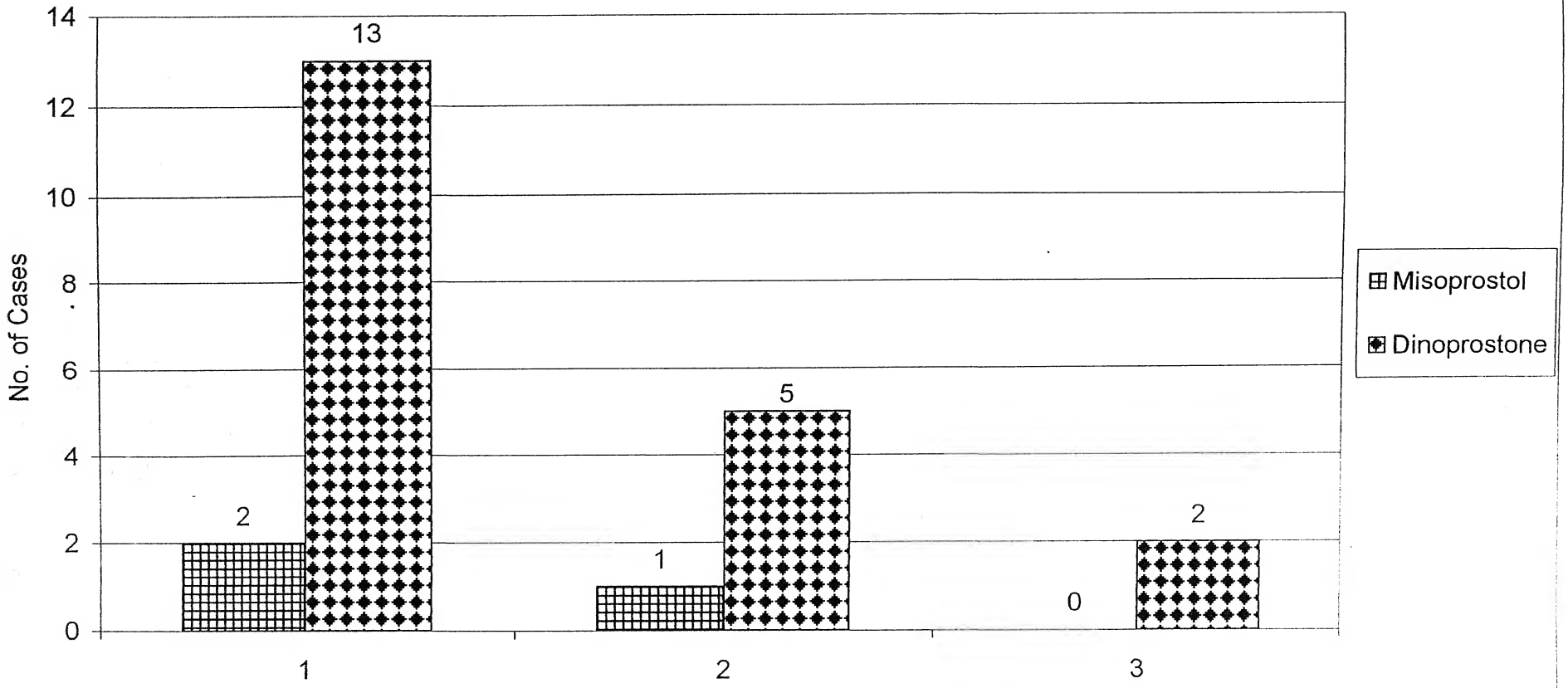
S. No	Method	Number of cases	
		Misoprostol	Dinoprostone
1	High doses of oxytocin	2	13
2	Surgical evacuation under oxytocin	1	5
3	Hysterotomy with ligation	0	2

The above table shows that with high doses of oxytocin 2 cases in misoprostol, group and 13 cases in dinoprostone group aborted. Surgical evacuation under oxytocin was used for 1 case in misoprostol group and 5 cases in dinoprostone group. Hysterotomy with ligation was employed as last resort for 2 cases in dinoprostone group.

SHOWING TOTAL DOSAGE OF DINOPROSTONE USED IN ABORTIONS



SHOWING MODE OF MANAGEMENT OF FAILED CASES



1. High doses of oxytocin.
2. Surgical evacuation under oxytocin.
3. hysterotomy with ligation

DISCUSSION

DISCUSSION

Medical termination of pregnancy has been the topic of discussion since long time, but recently it has gained much attention because of population explosion. Thus there should be a safe, cheap, easy and effective method to control this explosion problem to some extent. Thus it is the duty of medical personnel to sort out such a method of termination of pregnancy.

In 1971 **Stallworthy** mentioned 'no operation is so simple that it is entirely free from risks'. Thus it is the duty of every medical man to judge which method is safe for termination and to avoid the procedure all together, if it is hazardous to the life of patients.

Thus, a clinical evaluation of various methods of termination of pregnancy in second trimester has been attempted to judge their safety and reliability. A meticulous study in search of a safe alternative for mid trimester abortion has been carried out in Maharani Laxmi Bai Medical College, Jhansi in department of Obstetric and Gynaecology. This study was conducted on 240 patients who came for termination between 12-20 wks of gestation. Patients were divided randomly into 2 groups of 120 each and named as group A and group B. The study includes termination by serial use of 400 μg 4 hourly misoprostol vaginally in group A patients and comparing the results with serial use of dinoprostone 0.5mg 12 hourly intra-cervically in group B patients.

The efficacy of methods was observed. The observations were noted in terms of age, parity, and period of gestation, marital status,

socio-economic status, induction-abortion interval, doses of prostaglandin required, their success rates and appearance of side effects if any.

Relation to age

In study group the age group ranged from 18-45 yrs in misoprostol group. The majority of patients were in age group 25-30 yrs (40%) only 10% were in age groups above 35 yrs, with 40-45 yrs age group being least common and only 2% were in this age group. 18-25 yrs age group constituted 25% of group A.

In dinoprostone group also majority of patients were in age group 25-30 yrs (43.33%) and only 8.33% were in age groups above 35 yrs. 18-25 yrs age group constituted 23.33% of group B.

Relation to parity

In our study of mid-trimester abortion maximum patients were multipara. As shown in table III in misoprostol group, maximum patients were of parity-3 (32.5%) closely followed by parity-2 (28.33%) and parity-4 (25%). Least common was parity-1 (2.5%) parity-5 was (5%) and nulliparae were (6.66%).

In dinoprostone group again parity-3 was most common (33.33%) followed by parity-2 (25%) and parity-4 (23.33%) Parity-1 was least common (3.33%) and nulliparae were 8.33%.

Relation with marital status

In present study maximum patients were married 68.33% and 72.66% in misoprostol and dinoprostone group respectively. Unmarried patients in group A and group B were 18.03% and 15.83% respectively. Widows and divorcee were 13% and 12.5% respectively.

Relation to rural and urban population

68.33% of our patients were from rural areas, and 31.66% were from urban areas in group A and for group B the percentages were 66.66% and 33.33% respectively. Above data shows that the rural population came late for abortion because of hesitation and lack of education while urban population undergoes first trimester abortion if needed and only a few number of cases came in second trimester for abortion.

Relation to socio-economic status

In our study 56.66% patients belonged to low socio-economic status and 25% to middle class and 18.33% to high class in misoprostol group compared to 60%, 23.33% and 16.66% of low, middle and high class in dinoprostone group.

Relation of period of gestation

In present study in 12-14 weeks, 14-16, weeks, 16-18 weeks and 18-20 weeks gestational age group in group A and B following percentages of patients were seen 18.33%, 17.50%; 24.16; 22.50; 32.50, 33.33; 25, 26.66 respectively.

Thus the data shows that maximum number of patients came later weeks of pregnancy because of lack of education in rural areas.

Relation of induction-abortion interval

Induction-abortion interval is the time from application of first dose of misoprostol or dinoprostone to abortion.

In our study the mean induction abortion interval was 11.2 hours for misoprostol group and 18.1 hours for dinoprostone group.

The mean induction-abortion interval by misoprostol administered vaginally as reported by different authors in different studies is -

Bugalho et al in 1993 reported mean induction-abortion interval of 14.3hours while using misoprostol vaginally every 24 hourly (dose 200-800μg).

Jain and **Mishell**, in 1994 reported mean induction-abortion interval of 12 hours while using misoprostol 200 μg 12 hourly.

Srisomboon et al in 1997 reported mean induction-abortion interval of 27.5hrs while using 200 μg cervico vaginal misoprostol 12 hourly.

N.R. Agarwal et al (1996) reported mean induction-abortion interval of 14.4 hours using misoprostol 100μg 3 hourly and 25.6 hours using dinoprostone 0.5mg 12 hourly.

Carbonell et al in 1998 reported mean induction-abortion interval of 9.1 hours while using 8oo μg vaginal misoprostol 24 hourly for 3 doses.

Dickinson et al in 1998 reported mean induction-abortion interval of 16.9 hours while using 200 μg vaginal misoprostol 6 hourly for 4 doses.

Herabutya et al in 1998 reported mean induction abortion interval of 33.4 and 22.3 hours while using 400μg and 600μg vaginal misoprostol 12 hourly for 48 hours.

Wong et al in 1998 reported mean induction abortion interval of 14.1 hours using 400μg vaginal misoprostol 3 hourly for 5 doses.

Dickinson et al in 2002 reported mean induction abortion interval of 18.2, 15.1 and 13.2 hours while using 200μg vaginal misoprostol 6 hourly, 400μg vaginal misoprostol 6 hourly and 200μg

vaginal misoprostol 6 hourly (following a loading dose of 600μg) respectively.

Success rate

The success rate in present study was 97.5% for misoprostol and 83.33% for dinoprostone group.

Jain and **Mishell** in 1994 had a success rate of 89% within 24 hours using 200μg vaginal misoprostol 12 hourly.

N.R. Agarwal et al (1996) had a success rate of 90% in 24 hours using 100μg misoprostol 3 hourly and success rate was 80% using dinoprostone 0.5mg 12 hourly.

Batioglu et al in 1997 reported success rate of 92.9% within 48 hours 200μg oral misoprostol 1 hourly for maximum of 6 doses.

Carbonell et al reported success rate of 80% with 800μg vaginal misoprostol 24 hourly for 3 doses.

Dickinson et al in 1998 reported 74.9% success rate within 24 hours using 200μg vaginal misoprostol 6 hourly for 4 doses.

Herabutya et al in 1998 reported 82% success rate within 48 hours using 400μg vaginal misoprostol 12 hourly.

Wong et al in 1998 reported 80% success rate within 24 hours using 400μg vaginal misoprostol 3 hourly for 5 doses.

Dickinson et al in 2002 reported 76% success rate within 24 hours using 400 μg vaginal misoprostol 6 hourly.

Side effects

The incidence of side effects with both the groups was not very significant and in majority the side effects were of minor variety.

Nausea, vomiting and diarrhoea were more commonly seen in dinoprostone group.

Fever was more common in misoprostol group (7.5%) compared dinoprostone group (1.66%).

Severe uterine pain was more common in dinoprostone group (12.5%) compared to misoprostol group (7.5%).

Bleeding per vaginium during pre-abortion process was more commonly seen in misoprostol group (12.5%) compared to dinoprostone group (2.5%).

None of the patient required blood transfusion or resuscitation because of the bleeding.

Total dose requirement

The total dose requirement for abortion was in majority (55.66%) 800μg, i.e. 2 times application of 2 tablets of 200 μg each, for misoprostol group.

For dinoprostone group the most common dose requirement was 1 mg (66%), i.e. 2-time application of 0.5 mg each.

Mode of management of failed cases

In 2 of the misoprostol group and 13 of the dinoprostone group of the failed cases high doses of oxytocin resulted in abortion in both cases.

In 1 case in misoprostol group and 5 cases in dinoprostone group surgical evacuation under high doses of oxytocin was employed.

In 2 cases of the dinoprostone group hysterotomy with ligation was employed for abortion.

CONCLUSION

SUMMARY AND CONCLUSION

The present study was conducted in the Obstetrics and Gynaecology department of M.L.B., Medical College Jhansi on 240 patients admitted for mid-trimester abortion.

Total number of patients were divided into two groups A and B of 120 each.

The age group, parity, socio-economic status, urban-rural status, gestational age and marital status was comparable in both the groups.

Group A patients were applied 400μg misoprostol vaginally 4 hourly for a maximum of 5 doses and group B patients were applied 0.5 mg of dinoprostone gel 12 hourly for a maximum of 3 doses.

The mean induction-abortion interval in misoprostol group was 11.2 hours and 18.1 hours for dinoprostone group. The success rate within 40 hours was 97.5% for misoprostol and 83.33% for dinoprostone group. Side effects in both the groups were of minor degree and not very common.

There were in total 3 failed cases in misoprostol group and 20 failed cases in dinoprostone group.

The failed cases were managed in majority with high doses of oxytocin. Some cases required surgical evacuation under high dose of oxytocin. 2 cases of dinoprostone group required hysterotomy with ligation as the final management for the purpose of abortion.

From this study use of misoprostol in doses of 400μg 4 hourly (maximum 5 doses) proved to be much superior to dinoprostone in 0.5 mg 12 hourly doses (max 3 doses).

Increasing the dose from traditional use of 100 μg or 200 μg to 400 μg and reducing the dose interval from 24 hourly, 12 hourly or 6

hourly to 4 hourly resulted in increased efficacy as seen in our study. Moreover, in this study misoprostol was used in powder form after crushing the tablets and placing the powder in posterior fornix and then placing a normal saline swab. This method of application seems to have increased the efficacy of misoprostol.

Thus, we reach the conclusion that misoprostol (PGE_1) as compared to dinoprostone (PGE_2) for mid-trimester abortion is more effective, less costly, and easy to administer, easy to store and associated with fewer adverse effects.

BIBLIOGRAPHY

BIBLIOGRAPHY

1. Ashok PW, Templeton A : Non-surgical mid-trimester termination of pregnancy, a review of 500 consecutive cases. Br J Obstet and Gynecol; 106(7):706-10, 1999.

2. Auntry AM, Hayes EC, Jacobson GF, Kirby RS : A comparison of medical induction and dilation and evacuation for second trimester abortion. Am J Obstet Gynecol; 187(2):393-7, 2002.

3. Baird DT : Medical abortion in the first trimester. Best Prac Res Clin Obstet Gynecol; 16(2):221-36, 2002.

4. Batioglu S, Tongue E, Haberal A, Celikkanant H, Bagis T : Mid-trimester termination of complicated pregnancy with oral misoprostol. Adv Contracept; 13:55-61, 1997.

5. Berghahn L, Christensen D, Droste S : Uterine rupture during second-trimester abortion associated with misoprostol. Obstet and Gynecol: 98(5 Pt 2):976-7, 2001.

6. Berman R, Hale RW, Reich LA, Intra-amniotic prostaglandin F_2 alpha for induction of mid-trimester termination of pregnancies. Contraception; 9:635, 1974.

7. Blanchard K, Clark S, Winikoff B, Gaines G : Misoprostol for women's health: A review. Obstet Gynecol; 99(2):316-32, 2002.

8. Bradley LD : Complications in hysteroscopy : Prevention, treatment and legal risk. Curr Opin Obstet Gynecol; 14(4):409-15, 2002.

9. Brenner WE, Zuspan K : Synthetic laminaria for cervical dilatation prior to vaccum aspiration in mid-trimester pregnancy. Am J Obstet Gynecol, 143:745, 1982.

10. Bughalo A, Bique C, Almeda L, Faundes A : The effectiveness of intra vaginal misoprostol in inducing abortion after eleven weeks of pregnancy. Stud Fam Plann; 243:19-23, 1993.

11. Carbonell JL, Valera L, Velazeo A, Tanda R, Sanchez C : Vaginal misoprostol for early second trimester abortion. Eur J Contracept Reprod Health Care; 3(2):93-98, 1998.

12. Chang Y, Chen W, Yu M, Liu H : Intra-cervical misoprostol and prostaglandin E2 for labor induction. Int J Gynecol Obstet; 80(1):23-28, January 2003.

13. Cheng L : Termination of 10-16 weeks gestation with mifepristone plus misoprostol: A multi-centric randomised clinical trial. Zhonghua Fu Chan Ke Za Zhi; 34(5):268-71, 1999.

14. Chia KV, Ogbo VI : Medical termination of missed abortion. J Obstet Gynecol; 22(2):184-6, 2002.

15. Chittacharoen A, Herabutya Y, Punyavachira P : A randomized trial of oral and vaginal misoprostol to manage delivery in

cases of fetal death. Obstet Gynecol; 1-1(1):70-3, January 2003.

16. Dallenbach P, Boulvain M, Viardot C, Irion O : Oral misoprostol or vaginal dinoprostone for labor induction. A randomized controlled trial. Am J Obstet Gynecol; 188(1):162-7, January 2003.

17. Dutta H, Konar M, Chanda CK : A study of medical termination of pregnancy – 6071 cases. J Obstet Gyne Ind; 27:637-44, 1977.

18. Dickinson JE, Evans SF : The optimization of intra-vaginal misoprostol dosing schedules in second-trimester pregnancy termination. Am J Obstet Gynecol; 186(3):470-4, 2002.

19. Dickinson JE, Godfrey M and Evans SF : Efficacy of intravaginal misoprostol in second trimester pregnancy termination; A randomized controlled trail. J Matern Foetal Med; 7:115-19, 1998.

20. Duenhoelter JH, Gant NF, Jiminez JM : Concurrent use of prostaglandin F_2 alpha and laminaria tents for induction of mid-trimester abortion. Obstet Gynecol; 47:469-72, 1976.

21. Elisheikh A, Antasaklis A, Mesogistis S, Papantoniou N, Rodolakis A, Vogas E, Michalas S : Use of misoprostol for the termination of pregnancies. Arch Gynaecol Obstet; 265(94):204-6, 2001.

22. Ellertson C, Waldman SN : The mifepristone- misoprostol regimen for early medical abortion. Curr Women's Health Rep; 1(3):184-90, 2001.

23. El-Refaey H, O'Brien P, Morafa W, Walder J, Rodeck C : Use of misoprostol in the prevention of post partum hemorrhage. BJOG; 104:336-9, 1997.

24. Eng NS, Guan AC : Comparative study of intravaginal misoprostol with gemeprost, an abortifacient in second trimester missed abortion. Aust NZJ Obstet Gynecol; 37(3):331-34, 1997.

25. Fung TM, Lam MH, Wong SF et al : A randomized placebo-controlled trial of vaginal misoprostol for cervical priming before hysteroscopy in post menopausal women. BJOG; 109(5):561-5, 2002.

26. Fylling P, Refsdal A : Rivonal induced mid-trimester abortion. Arch Gynecol; 215:359, 1973.

27. Gilbert A, Reid R : A randomized trial of oral versus vaginal administration of misoprostol for the purpose of mid-trimester termination of pregnancy. Aust NZJ Obstet Gynecol; 41(4):407-10, 2001.

28. Golberg AB, Greenberg MB, Darney PD : Misoprostol and Pregnancy. N Engl J Med; 344:38-60, 2001.

29. Golbus MS : Laminaria and intra amniotic prostaglandin F_2 alpha for induction of mid-trimester abortion. Am J Obstet Gynecol; 119:569, 1974.

30. Gonjalez JA, Carlan SJ, Aversion MW : Out patient second trimester pregnancy termination. Contraception; 63(2):89-93, 2001.

31. Grimes DA : Clinicians who provide abortion, the thinning ranks. Obstet Gynecol; 80:719-23, 1992.

32. Gulmezoglu AM, Forna F, Villar J et al : Prostaglandins for prevention of post-partum hemorrhage (Cochrane review). Cochrane Database Syst Rev; (3): CD 0000494, 2002.

33. Haider S, Fekkih M, Chaieb A, Mellouli R, Khairi H : Oxytocin and misoprostol administrated intra vaginally for termination of pregnancy at 13 to 29 weeks of amenorrhea: A prospective randomized trial. J Gynecol Obstet Biol Reprod; 30(5):439-43, 2001.

34. Hall R, Duarte-Gardea M, Harlass F : Oral versus vaginal misoprostol for labor induction. Obstet Gynecol; 99(6):1044-8, 2002.

35. Herabutya Y, Israngura Na, Ayud Thaya N : Mid-trimester abortion using prostaglandin gel. Int J Gynecol Obstet; 34(2):169-73, 1991.

36. Herabutya Y, Chanrachakul B, Punyavachira P : Second trimester pregnancy termination: a comparison of 600 and 800

micrograms of intra vaginal misoprostol. J Obstet Gynecol Res; 27(3):125-28, 2001.

37. Herabutya Y, Chanrachakul B, Punyavachira P : Vaginal misoprostol in termination of second trimester pregnancy. J Gynecol Obstet Res; 26(2):121-25, 2000.

38. Herabutya Y, O-Prasertsawat B, Punyavachira P : Second trimester abortion using intra vaginal misoprostol. Int J Gynecol Obstet; 60:161-65, 1998.

39. Ho PC, Ngai SW, Liu KL, Wong GC, Lee SW : Vaginal misoprostol compared with oral misoprostol in termination of second trimester pregnancy. Obstet and gynecol; 90(5):735-38, 1997.

40. Ho PC, Tsang SS, Ma HK : Reducing the induction to abortion interval in termination of second trimester pregnancies : A comparison of mifepristone with laminaria tent. Br J Obstet and Gynecol; 102(8):648-51, 1995.

41. Hofmeyr GJ, Gulmezoglu AM : Vaginal misoprostol for cervical ripening and induction of labor. Cochrane Database Syst Rev; (1):CD 000941, 2003.

42. House Committee on Government Reform and Oversight : Off-label drug use and FDA review of supplemental drug applications: Hearing before the sub committee on human resources and inter governmental regulations. 104th Congress, 2nd session, 53-94, September 12, 1996.

43. Ingemansson CA : Legal abortion by extra amniotic instillation of Rivonal in combination with rubber catheter insertion in the uterus after the12th week of pregnancy. Am J Obstet Gynecol; 115:21, 1973.

44. Jain JK, Dutton C, Harwood B, et al : A prospective randomized, double-blinded, placebo-controlled trial comparing mifepristone and vaginal misoprostol alone for elective termination of early pregnancy. Hum Reprod; 17(6):1477-82, 2002.

45. Jain JK, Kuo J, Mishell DR Jr : A comparison of two dosing regimens of intra vaginal misoprostol for second trimester of pregnancy termination. Obstet Gynecol; 93(4):571-75, 1999.

46. Jain JK, Mishell DR Jr : A comparison of misoprostol with and without laminaria tents for induction of second trimester abortion. Am J Obstet Gynecol; 175:173-77, 1996.

47. Jain JK, Mishell Dr Jr.: A comparison of intra vaginal misoprostol with prostaglandin E_2 for termination of second trimester pregnancy. N Engl J Med; 331(5):290-93, 1994.

48. Johnson N : Intra cervical tents, usage and mode of action. Obstet Gynecol Surv; 44:410-20, 1989.

49. King TM, Bubin NH, Atienza MF, Burkman RT, Blake DA, Baros NA : Intra-amniotic urea and PG F_2 for mid-trimester abortion. Am J Obstet Gynecol; 129:817-824, 1977.

50. Kl Refaey H, Calder L, and Wheatlay DN. Templeton A : Cervical priming with prostaglandin E_1 analogue misoprostol & gemeprost. Lancet; 343:1207-09, 1994.

51. Kovavisarach E, Sathapanachai U : Intra vaginal 400 µg misoprostol for pregnancy termination in cases of blighted ovum: A randomized controlled trial. Aust NZ J Obstet Gynecol; 42(2):161-3, 2002.

52. Krofta L, Calda P, Zizka Z, Hruskova H, Kapras J : Termination of pregnancy in the second trimester using intra-amniotic administration of prostaglandins. Ceska Gynecol; 63(5):414-17, 1998.

53. Lee CN, Cheng WF, Lai HL, Shyu MK, Chen TM, Wu RT, Shih JC, Hsieh FJ : Comparison between intra venous PGE_2 a installation for termination in second trimester pregnancy. Journal of maternal-foetal investigation; 8(3):134-38, 1998.

54. Lipitz S, Grisaru D, Libshiz A, Rotstein Z, Schiff E, Lidor A, Achiron R : Intra amniotic prostaglandin F_2 alpha for pregnancy termination in the second and early third trimester of pregnancy. J Reprod Med; 42 (4):235-38, 1997.

55. Liu H.S, Chang YK, Chu TY, Yu MH, Chen WH. Extra amniotic balloon with PGE_2 versus extra ovular foley catheter with PGF2 α in mid-trimester therapeutic termination of pregnancy. Trop Doct; 31(3):157-61, 1998.

56. Mendilcioglu I, Simsek M, Seker PE, Erbay O, Zorlu CG, Trak B : Misoprostol in second and early third trimester for

termination of pregnancies with fetal anomalies. Int J Obstet Gynecol; 79:131-5, November 2002.

57. Mendilcioglu I, Zorlu CG, Simek M : Successful termination of a cervical pregnancy with misoprostol. Eur J Obstet Gynecol Reprod Biol; 106(1):96, January 2003.

58. Mousa HA, Alfirevic Z : Treatment for primary post partum hemorrhage (Cochrane Review). Cochrane Database Syst Rev; (1):CD 003249, 2003.

59. Munthali J, Moodely J : The usage of misoprostol for mid-trimester therapeutic termination of pregnancy. Trop Doct; 1(3):157-61, 2001.

60. Nabriski SA, Kallmanovitch K, Lebal R, Bodman O : Extra ovular trans cervical injection of rivanol for interruption of pregnancy. Am Obstet Gynecol; 110:54-56, 1971.

61. Oboro VO, Tabowei TO, Bosah JO : Intrauterine misoprostol for refractory post partum hemorrhage. Int J Gynecol Obstet; 80(1):67-68, January 2003.

62. Office for National Statistics : Abortion Statistics 1995. (England and Wales) (Series AB No. 22) London; HMSO: 1997.

63. Owen J, Hauth JC : Vaginal misoprostol vs concentrated oxytocin plus low dose prostaglandin E_2 for second trimester pregnancy termination. J Maternal Foetal Med; 8:48-50, 1999.

64. Pajak J, Tomialowics M, Florjanski J, et al : Comparison of vaginal misoprostol and oxytocin for labor induction in post-term pregnancy. Ginekol Pol; 72(12A):1300-4, 2001.

65. Parfitt K. Martindale: The complete drug reference. 32nd edition, London: Pharmaceutical Press; 1419-3, 1999.

66. Parikh MN, Parikh F : Aspirotomy (an outpatient technique for terminating second trimester pregnancy). In: Chakrabarty BK, Duttagupta H, Eds. Manual on Medical termination of pregnancy, 2nd ed. MTP committee of FOGSI Calcutta; 23:133-38, 1993.

67. Peterson WF, Berry N, Grace MR, Gulbranson CL : Second trimester abortion by dilatation and evacuation, an analysis of 11747 cases. Obstet Gynecol; 62:185-90, 1983.

68. Pongsatha S, Sirisukkasem S, Tongsong T : A comparison of 100 µg oral misoprostol every 3 hours and 6 hours for labor induction: A randomized controlled trial. J Obstet Gynecol Res; 28(6):308-12, 2002.

69. Pongsatha S, Tongsong T, Suwannawut O : Therapeutic termination of second trimester pregnancy with vaginal misoprostol. J Med Assoc Thai; 84(4):515-19, 2001.

70. Pongsatha S, Tongsong T : Misoprostol for second trimester termination of pregnancies with prior low transverse cesarean section. Int J Gynecol Obstet; 80(1):61-62, January 2003.

71. Pongsatha S, Tongsong T : Second trimester pregnancy termination with 800 μg vaginal misoprostol. J Med Assoc Thai; 84(6):859-63, 2001.

72. Rayburn WF : A physician's perspective to prescribe drugs for off-label uses during pregnancy. Obstet Gynecol; 81:1052-5, 1993.

73. Rodger MW, Braid DT : Pre treatment with mifepristone reduces interval between prostaglandin administration and expulsion in second trimester abortion. Br J Obstet and Gynecol; 97(1):41-5, 1990.

74. Roux PA, Tregoing SK, Zinn PM, Van Spuy ZM : Inhibition of progesterone secretion with trilostane for mid-trimester termination of pregnancy: Randomized controlled trials. Hum Reprod; 17(6):1483-9, 2002.

75. Royal College of Obstetricians and Gynaecologists: Induced abortion guideline No. 11, London; RCOG, 1997.

76. Sanchez-Ramos L, Danner CJ, Delke I et al : The effect of tablet moistening on labor induction with intravaginal misoprostol: a randomized trial. Obstet Gynecol; 99(6): 1080-4, 2002.

77. Sharma S, El-Rafaey H : The use of misoprostol as a cervical ripening agent in operative hysteroscopy. Am J Obstet Gynecol; 188(1); 297-8, January 2003.

78. Shetty A, Mackie L, Danielian P et al : Sublingual compared with oral misoprostol in term labor induction: A randomized controlled trial. BJOG; 109(6): 645-50, 2002.

79. Shetty A, Martin R, Danielian, et al : A comparison of two dose regimens of oral misoprostol for labor induction at term. Acta Obstet Gynecol Scand; 81(4):337-42, 2002.

80. Shubert W, Cullberg G : Second trimester abortion by rivonal with or without cervical dilators. Acta Obstet Gynecol Scand; 66:549-50, 1987.

81. Simsomboon J, Tongsong T, Pongisuttinum S : Termination of second trimester pregnancy with intra cervicovaginal misoprostol. J Med Assoc Thai; 80:141-46, 1997.

82. Srisomboon J, Pongisuttinum S : Efficacy of intra cervicovaginal misoprostol in second trimester pregnancy termination. A comparison between live and dead fetuses. J Obstet Gynecol Res; 24(1):1-5, 1998.

83. Tang OS, Ho PC : Medical abortion in second trimester. Best Pract Res Clin Obstet Gynecol; 16(2):237-46, 2002.

84. Tang OS, Ho PC : Medical abortion in the second trimester. Best Pract Res Clin Obstet Gynecol; 237-46, 2002.

85. Tang OS, Ho PC : Pilot study on the use of sub lingual misoprostol for medical abortion. Contraception; 64(5):315-7, 2001.

86. Tang OS, Lau WN, Ng EH, Lee SW, Ho PC : A prospective randomized study to compare the use of repeated doses of vaginal with sublingual misoprostol in the management of first trimester silent mis carriages. Hum Repord; 18(1):176-81, January 2003.

87. Tang OS, Thong KJ, Baird DT : Second trimester medical abortion with mifepristone and gemeprost : A review of 956 cases. Contraception; 64(1):29-32, 2001.

88. Tang OS, Xu J, Cheng L et al : Pilot study on the use of sublingual misoprostol with mifepristone in termination of first trimester pregnancy up to 9 weeks gestation. Hum Reprod; 17(7):1738-40, 2002.

89. Thomas JA, Leyland N, Durand N et al : The use of oral misoprostol as a cervical ripening agent in operative hysteroscopy : A double-blind, placebo-controlled trial. Am J Obstet Gynecol; 186(5):876-9, 2002.

90. Thong KJ, Baird DT : A study of gemeprost alone, dilapan or mifepristone in combination with gemeprost for the termination of second trimester pregnancy. Contraception; 46(1):11-17, 1992.

91. Todd CS, Soler M, Castleman L, et al : Buccal misoprostol as cervical preparation for second trimester pregnancy termination. Contraception; 65(6):415-8, 2002.

92. Toppozada M, Ismail AA : Intra uterine administration of drugs for termination of pregnancy in the second trimester. Baillier's Clin Obstet Gynecol; 4:327-49, 1990.

93. Trasy SD, Batwar OD. Evaluation of ethacridine lactate followed by carboprost tromethamine by extra-amniotic route in midtrimester termination of pregnancy. J Obstet and Gyne Ind; 50(2):59-62, 2000.

94. Tsai EM, Yang CH, Lee JN : Medical abortion with mifepristone and misoprostol : A clinical trial in Taiwanese women. J Formos Med Assoc; 101(4):277-82, 2002.

95. United Nations Development Program / United Nations Fund for Population Activities / World Health Organization / World Bank Special Programme of Research Development and research Training in Human Reproduction. Annual Technical report 1997 Geneva: World Health Organization, 1998.

96. Urban R, Lemancewicz A, Urban J, et a : Misoprostol and dinoprostone therapy for labor induction : A Doppler comparison of uterine and fetal hemodynamic effects. Eur J Obstet Gynecol Reprod Biol; 106(1):20-24, January 2003.

97. Vlasova D, Tsankova M : The termination of the pregnancy in the second trimester with rivonal. Akush Ginekol (Sofia); 35(1-2):16-17, 1996.

98. Wagaarachchi PT, Ashok PW, Narvekar NN et al : Medical management of late intrauterine death using a combination of mifepristone and misoprostol. BJOG; 109(4):443-7, 2003.

99. Webster D, Penny GC, Templeton A : A comparison of 600 and 200 mg mifepristone prior to second trimester abortion with the prostaglandin misoprostol. Br J Obstet and Gynecol; 103(7):706-9, 1996.

100. Weinberg PC, Lin man JE, Linman SK : Intra-amniotic urea for induction of mid trimester pregnancy termination. Obstet Gynacol; 415:325-327, 1975.

101. Wing DA, Tran S, Paul RH : Factors affecting the likelihood of successful induction after intra vaginal misoprostol application for cervical ripening and labor induction. Am J Obstet Gynecol; 186(6):1237-40, 2002.

102. Wing DA : A benefit-risk assessment of misoprostol for cervical ripening and labor induction. Drug Saf; 25(9):665-76, 2002.

103. Winker CL, Gray AC, Hauth JC, Owen J, Tucker MJ : Mid-trimester labour induction : Concentrated oxytocin compared with prostaglandins E2 vaginal suppositories. Obstet Gynecol; 77:297-300, 1991.

104. Wong KS, Nagi CS, Yeo EL, Tang LC, Ho PC : A comparison of two regimens of intra vaginal misoprostol for termination second trimester of pregnancy : A randomized comparative trial. Hum Reprod; 15(30:709-12, 2000.

105. Wong KS, Ngai CSW, Wong AYK, Tang LCW, Ho PC : Vaginal misoprostol compared with vaginal gemeprost in

termination of second pregnancy: A randomized trial. Contraceptive; 58:207-10, 1998.

106. Wright Francis DL, Raynor BD, Webb GW : Misoprostol in second trimester termination of pregnancy. Prim Care Update Obstet & Gyns; 5(4):176-9, 1998.

107. Yadav S, Kapoor S, Kalra M, Das SK : Mid trimester termination of pregnancy improved outcome with extra-amniotic instillation of ethacridine lactate combined with syntocinon. J Obstet Gyne Ind; 43(5):668-72, 1993.

108. Yapar EG, Senoz S, Urkutur M, Batioglu S, Gokmen O : Second trimester pregnancy termination including foetal death : Comparison of five different methods. Eur J Obstet Gynecol Reprod Biol; 69:97-102, 1996.

MASTER CHART

MASTER CHART 'GROUP – A' (MISOPROSTOL)

S. No.	Age (yrs)	Parity	Marital status	Rural / Urban	Socio - economic status	Gestational age (weeks)	Induction abortion interval (hrs)	Side effects	Dose used (µg)
1	26	P_4	M	R	L	16-18	8	-	400
2	27	P_0	UM	U	M	12-14	8	F	800
3	18	P_0	UM	R	L	14-16	9	B	800
4	31	P_5	M	R	L	16-18	8	-	800
5	42	P_3	D	R	M	16-18	18	-	1200
6	27	P_4	M	R	L	12-14	8	N	400
7	33	P_2	M	R	L	18-20	9	-	800
8	18	P_0	UM	U	H	14-16	20	S	1600
9	26	P_2	M	R	M	18-20	30	-	1200
10	34	P_3	D	R	L	18-20	9	B	800
11	28	P_2	M	R	L	12-14	18	V	1200
12	20	P_5	M	R	L	16-18	8	-	800
13	28	P_1	M	U	M	14-16	F	-	800
14	29	P_1	M	R	M	16-18	9	B	2000
15	35	P_3	M	R	L	18-20	36	F	2000
16	22	P_0	UM	U	H	12-14	8	-	800
17	27	P_2	M	R	L	16-18	8	-	400
18	30	P_3	M	R	M	14-16	8	-	400
19	33	P_2	D	R	L	16-18	8	-	400
20	26	P_2	M	R	L	14-16	8	-	400
21	23	P_5	M	U	M	16-18	8	-	400

22	26	P_2	M	R	L	12-14	9	S	800
23	31	P_4	M	U	M	14-16	8	-	800
24	24	P_5	M	R	L	18-20	8	-	400
25	32	P_3	M	R	M	18-20	8	V	800
26	27	P_4	M	U	M	12-14	9	B	800
27	25	P_2	M	R	L	14-16	8	-	400
28	35	P_3	D	R	L	16-18	8	-	800
29	28	P_4	M	R	M	18-20	8	D	800
30	20	P_2	M	U	L	12-14	8	-	400
31	33	P_3	M	R	L	14-16	8	F	800
32	22	P_2	M	R	L	14-16	8	-	400
33	35	P_3	D	R	L	12-14	9	F	800
34	29	P_4	M	U	H	16-18	8	B	800
35	19	P_0	UM	R	L	18-20	8	S	400
36	33	P_3	M	R	M	14-16	8	-	800
37	18	P_0	UM	U	L	16-18	8	-	800
38	32	P_3	M	R	L	14-16	8	-	800
39	30	P_2	D	R	L	12-14	9	B	800
40	20	P_0	UM	U	H	18-20	8	-	800
41	35	P_3	M	R	H	18-20	8	D	400
42	27	P_2	D	R	L	16-18	9	-	800
43	22	P_0	UM	U	M	14-16	8	S	800
44	31	P_3	M	U	H	12-14	8	F	400
45	28	P_2	D	R	L	18-20	9	-	800
46	25	P_4	M	R	L	14-16	8	-	800
47	27	P_3	M	R	L	16-18	8	-	800
48	31	P_4	M	R	L	14-16	8	B	800
49	26	P_2	M	U	H	16-18	18	-	800

50	36	P_4	M	R	L	18-20	8	-	400
51	22	P_2	M	R	M	14-16	9	S	800
52	33	P_3	W	R	L	16-18	30	-	1600
53	38	P_4	M	U	L	16-18	8	-	800
54	27	P_2	M	R	M	18-20	9	N	800
55	21	P_5	M	R	L	16-18	8	B	400
56	35	P_3	M	U	H	12-14	18	-	1200
57	29	P_2	M	R	L	18-20	8	-	800
58	39	P_4	M	U	H	14-16	30	F	2000
59	20	P_2	M	U	M	16-18	9	-	800
60	33	P_3	W	R	L	18-20	8	S	400
61	30	P_2	M	R	L	12-14	8	B	800
62	40	P_4	M	U	M	16-18	8	-	400
63	19	P_0	UM	R	L	18-20	8	-	800
64	26	P_2	M	R	L	14-16	8	-	800
65	32	P_3	M	U	L	16-18	8	-	400
66	28	P_4	M	U	L	14-16	8	-	800
67	22	P_2	M	R	L	18-20	10	B	800
68	29	P_3	W	U	H	12-14	8	-	400
69	21	P_4	M	R	L	18-20	9	D	800
70	33	P_3	M	U	M	16-18	8	-	800
71	30	P_2	M	R	L	12-14	9	N	800
72	23	P_2	M	U	M	14-16	9	F	800
73	27	P_3	W	R	L	18-20	10	B	800
74	28	P_2	M	U	L	14-16	11	V	800
75	22	P_2	M	R	M	12-14	11	S	800
76	26	P_2	M	U	H	16-18	20	-	1200
77	21	P_4	M	R	L	14-16	F	-	800

78	26	P_2	M	R	L	18-20	8	-	400
79	30	P_3	M	U	H	18-20	8	-	800
80	29	P_2	M	R	L	16-18	18	-	1200
81	34	P_3	W	R	M	12-14	30	B	1200
82	28	P_2	M	U	H	16-18	8	-	800
83	22	P_4	M	R	L	14-16	18	S	1200
84	33	P_3	M	R	L	12-14	8	-	400
85	28	P_3	M	U	H	16-18	8	D	800
86	27	P_3	M	R	M	18-20	30	-	1600
87	23	P_4	M	R	M	16-18	18	-	1200
88	26	P_2	M	U	H	12-14	8	-	400
89	35	P_3	M	R	L	14-16	8	-	800
90	26	P_3	M	U	H	14-16	F	-	2000
91	21	P_0	M	R	L	16-18	8	-	800
92	26	P_4	M	U	M	12-14	18	B	1200
93	27	P_3	M	R	M	16-18	8	D	800
94	33	P_3	W	R	L	16-18	30	-	2000
95	28	P_4	M	U	H	18-20	8	S	400
96	27	P_3	M	R	L	12-14	18	-	1200
97	19	P_0	UM	U	H	16-18	8	-	800
98	29	P_3	M	R	M	14-16	8	B	400
99	34	P_3	M	R	L	16-18	8	-	800
100	28	P_4	M	R	L	16-18	30	-	1600
101	30	P_3	M	U	H	18-20	18	-	1200
102	24	P_4	M	R	L	16-18	8	-	400
103	32	P_3	M	R	L	18-20	18	-	1600
104	26	P_0	UM	R	L	14-16	8	-	400
105	34	P_3	M	U	H	18-20	18	-	1600

106	35	P_3	M	R	L	14-16	8	F	800
107	22	P_4	M	U	M	16-18	8	-	800
108	28	P_5	M	R	L	12-14	8	D	400
109	27	P_4	W	R	L	16-18	18	-	1200
110	33	P_3	M	U	H	18-20	8	-	800
111	44	P_4	M	R	L	16-18	8	B	800
112	33	P_4	M	R	M	14-16	8	-	400
113	21	P_0	UM	R	L	16-18	18	F	1200
114	37	P_5	M	U	H	12-14	8	-	800
115	34	P_3	M	R	M	18-20	8	-	800
116	35	P_3	M	R	L	18-20	18	-	1600
117	38	P_5	W	R	L	14-16	8	-	800
118	39	P_3	M	U	H	16-18	8	-	800
119	27	P_4	M	R	L	16-18	8	-	800
120	27	P_3	M	U	L	18-20	8	-	400

MASTER CHART 'GROUP – B' (DINOPROSTONE)

S. No.	Age (yrs)	Parity	Marital status	Rural / Urban	Socio - economic status	Gestational age (weeks)	Induction abortion interval (hrs)	Side effects	Dose used (ml)
1	18	P_0	UM	U	L	12-14	36	-	1
2	37	P_4	M	R	L	18-20	20	D	1
3	26	P_2	M	R	M	16-18	36	-	1
4	39	P_4	M	R	L	14-16	10	N	0.5
5	31	P_1	M	U	L	12-14	30	-	1
6	18	P_0	UM	U	M	18-20	F	S	F
7	37	P_4	M	R	L	16-18	11	F	0.5
8	33	P_2	D	U	L	14-16	20	B	1
9	39	P_4	M	R	M	12-14	18	N	1
10	35	P_2	M	R	L	18-20	10	-	1
11	20	P_3	UM	U	L	16-18	9	S	0.5
12	37	P_4	M	U	M	14-16	36	D	1.5
13	31	P_2	M	R	L	12-14	11	-	0.5
14	39	P_4	M	R	L	18-20	20	-	1
15	26	P_3	M	R	L	18-20	20	-	1
16	31	P_1	M	U	L	12-14	11	-	0.5
17	43	P_4	M	R	L	14-16	36	-	1.5
18	27	P_3	M	R	M	12-14	18	S	1
19	33	P_2	M	R	L	18-20	30	-	1
20	25	P_3	M	U	M	12-14	10	-	0.5
21	28	P_3	M	R	L	14-16	21	N	0.5

22	35	P_2	D	U	L	12-14	20	S	1
23	28	P_4	M	R	M	16-18	8	D	0.5
24	22	P_3	M	R	L	18-20	30	-	1
25	31	P_2	M	R	L	14-16	11	-	0.5
26	30	P_3	M	U	M	16-18	20	-	1
27	33	P_2	M	R	L	12-14	18	-	1
28	29	P_3	M	R	L	18-20	11	-	0.5
29	27	P_3	M	U	L	16-18	20	B	1
30	18	P_0	M	R	L	14-16	18	-	1
31	26	P_3	M	U	H	12-14	10	S	1
32	27	P_3	M	R	L	18-20	11	D	0.5
33	25	P_4	M	R	M	16-18	20	-	1
34	20	P_2	UM	U	H	14-16	18	N	1
35	26	P_3	M	R	L	12-14	8	-	0.5
36	27	P_3	M	R	M	16-18	9	-	0.5
37	22	P_2	UM	R	L	18-20	11	-	0.5
38	31	P_4	M	U	H	14-16	18	S	1
39	28	P_3	M	R	M	12-14	20	D	1
40	25	P_2	M	R	L	14-16	11	-	0.5
41	33	P_4	M	U	L	18-20	20	-	1
42	30	P_3	M	R	L	12-14	18	-	1
43	45	P_5	D	U	H	16-18	18	-	1
44	26	P_3	M	R	L	18-20	11	-	0.5
45	18	P_0	UM	R	L	16-18	30	-	1
46	35	P_4	W	U	M	14-16	20	S	1
47	26	P_3	M	R	L	12-14	11	-	0.5
48	20	P_3	UM	R	L	18-20	18	-	1
49	31	P_2	M	R	M	12-14	11	N	0.5

50	27	P_3	M	U	H	16-18	10	-	0.5
51	30	P_3	M	R	L	14-16	20	V	1
52	22	P_2	UM	R	L	18-20	8	-	0.5
53	28	P_4	M	U	M	12-14	11	-	0.5
54	33	P_3	M	R	L	14-16	18	D	1
55	31	P_2	M	U	H	16-18	30	-	1
56	27	P_2	M	R	L	18-20	11	-	0.5
57	35	P_4	W	R	L	16-18	30	-	1
58	25	P_2	M	R	M	18-20	11	-	0.5
59	30	P_3	M	R	L	12-14	18	S	1
60	31	P_4	M	U	M	14-16	10	-	0.5
61	29	P_3	M	R	L	12-14	20	-	1
62	25	P_2	M	R	L	18-20	11	N	0.5
63	33	P_4	M	U	M	16-18	30	-	1
64	26	P_2	M	R	L	16-18	18	V	1
65	29	P_3	M	R	L	14-16	11	-	0.5
66	20	P_2	UM	R	L	18-20	20	D	1
67	27	P_3	M	U	H	12-14	10	-	0.5
68	35	P_4	M	R	L	14-16	18	-	1
69	18	P_0	UM	R	L	16-18	11	-	1
70	28	P_3	M	U	M	18-20	30	-	1
71	20	P_0	UM	R	L	16-18	20	-	1
72	35	P_3	W	R	L	16-18	36	-	0.5
73	33	P_4	W	R	M	16-18	36	-	1
74	28	P_2	M	U	H	16-18	36	-	1.5
75	31	P_4	UM	R	L	18-20	36	-	1.5
76	26	P_3	M	U	M	16-18	18	S	1
77	18	P_0	UM	R	L	14-16	36	-	1.5

78	33	P_4	W	U	H	18-20	20	-	1
79	26	P_3	M	R	M	12-14	18	-	1
80	20	P_0	UM	R	L	16-18	10	N	1
81	30	P_2	M	R	L	14-16	11	-	1
82	26	P_3	UM	R	L	18-20	F	V	F
83	35	P_4	D	U	H	16-18	18	-	1
84	25	P_2	UM	R	M	14-16	36	S	1.5
85	31	P_3	M	R	L	12-14	F	-	F
86	28	P_3	M	U	H	16-18	F	-	F
87	27	P_2	M	R	L	14-16	18	-	1
88	31	P_3	M	R	L	18-20	11	-	1
89	22	P_3	UM	U	H	16-18	20	-	1
90	29	P_2	M	R	M	16-18	18	S	1
91	27	P_2	M	R	L	16-18	F	N	F
92	25	P_3	M	U	H	18-20	F	-	F
93	30	P_3	M	R	L	16-18	F	V	F
94	26	P_2	M	R	L	16-18	18	-	1
95	33	P_3	D	U	M	18-20	20	D	1
96	18	P_0	UM	R	L	14-16	F	S	F
97	28	P_2	M	U	H	16-18	18	-	1
98	29	P_2	M	R	L	18-20	F	-	F
99	20	P_0	UM	R	L	16-18	F	-	F
100	30	P_2	M	R	L	16-18	F	-	F
101	26	P_5	M	R	L	16-18	F	-	F
102	35	P_5	D	U	H	18-20	18	-	1
103	20	P_5	M	R	L	14-16	F	-	F
104	27	P_5	M	R	L	16-18	18	-	1
105	31	P_5	W	U	H	18-20	F	S	F

106	29	P_4	M	R	M	16-18	11	-	1
107	33	P_5	D	U	H	14-16	20	V	1
108	22	P_0	M	R	L	18-20	F	F	F
109	26	P_4	M	R	L	16-18	18	-	1
110	28	P_4	M	R	L	14-16	F	-	F
111	45	P_5	D	U	M	18-20	F	S	F
112	30	P_4	M	R	L	16-18	18	-	1
113	26	P_4	M	U	H	18-20	18	B	1
114	25	P_3	M	R	M	16-18	F	-	F
115	28	P_4	M	R	L	14-16	20	-	1
116	27	P_4	D	U	H	16-20	11	D	1
117	30	P_3	M	R	L	18-20	18	N	1
118	20	P_0	M	R	M	14-16	F	-	F
119	27	P_2	M	R	L	16-18	F	S	F
120	29	P_3	M	U	H	14-16	18	-	1

*

M – Married

D – Divorcee

UM – Unmarried

W – Widow

R – Rural

U – Urban

H – High socio-economic class

M – Middle socio- economic class

L – Low socio-economic class

F – In induction abortion interval

Group denotes 'failed case'

D – Diarrhea

N – Nausea

S – Severe uterine pain

F – Fever

B – Bleeding (excessive)

V - Vomiting